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EDITED BY

C. STEVEN RICHARDS &

MICHAEL W. O'HARA

The Oxford Handbook *of* DEPRESSION *and* COMORBIDITY

The Oxford Handbook of Depression and Comorbidity

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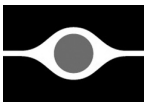

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Peter E. Nathan
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CONTENTS

CHAPTER

1 Introduction

C. Steven Richards *and* Michael W. O'Hara

Abstract

In this chapter, we provide a brief introduction to our book. We discuss the following themes, which run throughout this edited book on depressive disorders and comorbidity: assessment and diagnosis, theory and methods, psychiatric comorbidity, health comorbidity, relationship comorbidity, intervention and consultation, and future directions. A number of themes will be apparent, including the incredibly broad scope of depressive comorbidity. Depression goes with many other problems. Another theme is that the specifics of depressive comorbidity—and the implications for theory, research, and practice—vary considerably as we consider one type of comorbidity versus another. For example, the comorbidity of depression and generalized anxiety disorder has very different implications than the comorbidity of depression and alcohol-use disorder, which in turn is different than the comorbidity of depression and cancer, which again has different implications than the comorbidity of depression and severe relationship dysfunction. Each of the chapters in the book highlight some of the themes and issues, but the remarkable breadth and depth of depressive comorbidity becomes clearer as we consider all of the chapters in total. We attempt to bridge some of these differences and look for common themes in the Epilogue at the end of the book, as do some of the contributors in their individual chapters on specific issues or types of comorbidity. In this Introduction, however, we focus more on the specific chapters and a few of the themes that are highlighted in each one. Overarching themes, such as what is meant by *comorbidity*, how might future efforts at assessment and treatment be improved, and what future developments may be particularly helpful are discussed in many of the individual chapters. This brief introduction serves to highlight a few of the issues and introduce the reader to the broad array of chapters that await them in the rest of the book.

Key Words: introduction, assessment and diagnosis, theory and methods, psychiatric comorbidity, health comorbidity, relationship comorbidity, intervention and consultation, future directions

Depression is associated with many psychiatric disorders, chronic health problems, and severe dysfunction in close relationships. To observe that depression goes with many other problems may *appear* somewhat like observing that severe distress goes with many difficult challenges in life. This type of association and comorbidity seems almost ubiquitous. But we are not arguing that depression is a proxy measure for "severe distress." Depression and depressive comorbidity are much more complicated than that. Rather, we argue it is stunning that depressive disorders are comorbid with such a vast array of other psychiatric disorders, numerous health problems and diseases, and many types of severely dysfunctional relationships. This is part of why depressive comorbidity is so interesting—and important. With the 37 chapters that follow in this edited book, *The Oxford Handbook of Depression and Comorbidity*, some of the themes that are often discussed include assessment and diagnosis, theory and

methods, psychiatric comorbidity, health comorbidity, relationship comorbidity, intervention and consultation, and future directions.

Assessment, Diagnosis, Theory, and Methods

In chapters 2 through 5, the authors discuss themes of assessment, diagnosis, theory, and methods regarding depressive comorbidity. For example, in chapter 2, Widiger and Gore discuss assessment and diagnosis within the context of the various editions of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*), from the first edition in the 1950s (*DSM-I*) to the fifth, most recent revision in 2013 (American Psychiatric Association, 2013). Although most of the issues, findings, and implications for depressive comorbidity that are discussed in this book do not depend greatly on which edition of the *DSM* is being used, Widiger and Gore do explain and discuss how versions of the *DSM* may have some impact on our thinking about depressive comorbidity. The authors' particular emphasis, of course, is on the diagnosis of mood disorders such as depression (e.g., major depressive disorder [MDD]), which is virtually identical between the fourth (*DSM-IV*); fourth, text revision (*DSM-IV-TR*); and fifth (*DSM-5*) editions of the *DSM*, with the minor exception—in our opinion—for how "bereavement" is addressed in the diagnostic decision making regarding MDD (American Psychiatric Association, 1994, 2000, 2013). Widiger and Gore also discuss some important issues regarding definitions, empirical support, and theoretical models of classification.

In chapter 3, Markon discusses how theoretical, statistical, and methodological issues may influence our constructs and models of comorbidity. Using depressive and anxiety disorders as examples, Markon compares and contrasts two models of comorbidity: one that focuses on a *shared liability* for the comorbid disorders and another that focuses on *correlated symptoms* for the comorbid disorders. Markon uses these contrasted models to illustrate how our understanding of comorbidity can influence our understanding of psychopathology in general.

In chapter 4, Watson and Stasik discuss how analyzing the magnitude of distress and the specificity of comorbid symptoms may potentially improve assessment, diagnosis, and a more complete understanding of comorbidity. The authors use the specific psychiatric diagnoses of MDD and posttraumatic stress disorder (PTSD) to illustrate this approach. Moreover, Watson and Stasik place this discussion in the context of a conceptual model that Watson and his colleagues have developed called the Quadripartite Model. Furthermore, as with most of the chapters in this book, Watson and Stasik discuss some of the implications of their analysis for clinicians who are working with patients that exhibit depressive disorders and comorbidity.

In chapter 5, Eaton and Krueger provide a thorough discussion regarding assessment strategies in the context of depressive disorders, comorbidity, and the evidence for an "underlying internalizing disorder liability" that may explain some of the high comorbidity rates between depression and other psychiatric disorders. Eaton and Krueger also discuss some of the important implications for depressive comorbidity in the context of issues such as age, ethnicity, and psychometric concerns. This topic has received a considerable amount of empirical attention recently, and it is very much on the minds of researchers, scholars, and practitioners in the area (e.g., Eaton et al., 2013; Wright et al., 2013).

Comorbidity Between Depression and Another Psychiatric Disorder or Diagnosis

For chapters 6 through 17, the emphasis is on the comorbidity between depression—particularly MDD—and another specific psychiatric disorder or diagnosis. Thus, in chapter 6, Castriotta and Craske discuss the comorbidity of depression and panic disorder. They note that a majority of people with panic disorder also experience comorbidity with MDD, while a minority—but still a substantial number—of individuals with MDD also have comorbidity with panic disorder. Reflecting a theme that is present in virtually all of the chapters on psychiatric comorbidity, the specific comorbidity of depression and panic disorder usually predicts the following concerns: more severe symptoms; greater persistence of the disorders; additional treatment and follow-up challenges that are more difficult to manage than in cases in which the two disorders show little comorbidity; and very serious implications for an array of day-to-day functioning domains including work, home, and close relationships. Moreover, suicidal risk appears to increase with this type of comorbidity, which is also a concern that is mentioned in some of the other comorbidity chapters. In addition, Castriotta and Craske discuss important issues regarding the development of comorbid depression and panic disorder and research on evidence-based treatment of this comorbid condition.

In chapter 7, Najavits and Capezza discuss the comorbidity of depression and PTSD. Following a traumatic event, the comorbidity of PTSD and depression, especially MDD, is quite common. Najavits and Capezza discuss a wide range of relevant topics, including assessment, diagnosis, prevalence, risk factors, developmental issues, evidence-based interventions, and future research directions. They also focus on two areas that have received intense research attention: military traumas and interpersonal abuse. Najavits and Capezza discuss the practical implications for clinicians and some treatment recommendations. As with most types of depressive comorbidity, the authors note the likelihood that the comorbid condition will be harder to treat effectively, more prone to relapse and recurrence, and more likely to have a negative impact on daily living.

In chapter 8, Langer and Rodebaugh discuss the comorbidity of depression and social anxiety disorder. Comorbidity, in the form of co-occurrence, is common with these two disorders. Moreover, the presence of one disorder increases the risk for developing the other. Langer and Rodebaugh discuss evidence for a shared vulnerability factor regarding depression and social anxiety disorder, with genetic diatheses and traits such as positive and negative affect apparently playing a role in the high comorbidity rates. Langer and Rodebaugh also discuss some interesting research on coping efforts, including counterproductive efforts to cope with perceived social exclusion, which unfortunately may lead to yet higher levels of depression and social anxiety. In addition, the authors provide some recommendations for clinicians regarding effective methods for assessment, treatment, and follow-up.

In chapter 9, Mineka, Anand, and Sumner discuss the comorbidity of MDD and generalized anxiety disorder (GAD). This specific comorbidity topic, regarding MDD and GAD, has been one of the more active areas for theory and research, with a large number of theoretical papers and empirical studies published in the past 25 years. Mineka and colleagues discuss the overlap of symptoms; high rates of comorbidity; diagnostic considerations; and further implications for theory, research, and practice if GAD is continued to be classified as an anxiety disorder versus being classified as some type of mood or depressive disorder. The authors conclude that the evidence best supports continuing to classify GAD as an anxiety disorder, which is a conclusion also reached by the task forces and study groups who have developed *DSM-IV* (American Psychiatric Association, 1994), *DSM-IV-TR* (American Psychiatric Association, 2000), and *DSM-5* (American Psychiatric Association, 2013). Mineka and colleagues also provide a discussion of several types of comorbidity, including cross-sectional, cumulative or lifetime, and sequential. The authors conclude their chapter by discussing some of the implications for clinicians regarding assessment and treatment of comorbid MDD and GAD. Because the comorbidity of depressive and anxiety disorders presents additional treatment challenges for the patient and the clinician, combined treatments that include psychological and medication interventions are gaining in popularity among some research and practitioner groups (e.g., Wetherell et al., 2013). In addition, the relatively high comorbidity between MDD and GAD has led investigators to look for many common risk factors that might account for some of this high association. For instance, recent studies have identified "rumination" as a possible process that may link stressful life events to both depression and anxiety (e.g., Michl, McLaughlin, Shepherd, & Nolen-Hoeksema, 2013).

In chapter 10, Witkiewitz and Stauffer discuss the comorbidity of depression and alcohol-use disorder. The substance-related disorder discussed here falls under the grouping of substance-related and addictive disorders in *DSM-5* (American Psychiatric Association, 2013). Witkiewitz and Stauffer note large-scale surveys done by the World Health Organization and similar organizations usually find that alcohol-use disorders and depression rank very highly in lists of all-cause disability, with the World Health Organization findings suggesting that these risk factors may be as high as third and fourth among the probable risk factors for causing disease burden and disability. With a focus solely on disability, rather than also on disease burden and mortality, depression sometimes climbs to the number-one cause of day-to-day disability, in Western countries such as the United States and countries in western Europe. The authors discuss the frequent comorbidity of depression and alcohol-use disorders, along with recent research on symptoms; prevalence; risk and protective factors; development and course of the comorbid disorders; and the unfortunate prospect of more difficult assessment, treatment, outcome, and follow-up for patients with these co-occurring disorders. Witkiewitz and Stauffer also discuss a wide range of important treatment considerations for working with patients who have comorbid depressive and alcohol-use disorders, and they provide some recommendations for clinicians.

The relatively high comorbidity of depressive and alcohol-use disorders has led investigators, of course, to explore many possible explanations for these strong associations; these studies include looking for common liabilities and risks for the disorders, along with specific hypotheses such as alcohol-use being a coping strategy to "self-medicate" or cope with unpleasant negative affect such as depression (e.g., Crum et al., 2013).

In chapter 11, Keel and Holland discuss and evaluate the high comorbidity between depressive disorders such as MDD and eating disorders such as anorexia nervosa, bulimia nervosa, and binge eating disorder. The authors also explore how some of the substance-use disorders appear to play a role in shared liability, risk, and comorbidity. Perhaps few subtopics in psychopathology research have enjoyed as much research attention recently as the eating disorders. Therefore, Keel and Holland are able to discuss some recent empirically supported developments in our understanding of the high comorbidity of depression and eating disorders. For example, models of shared liability and high risk or diathesis for depressive disorders and eating disorders have received some mixed support, although this area is very complex, and inconsistent findings make it more challenging to untangle the various hypotheses and results. Keel and Holland also discuss some of the clinical issues regarding the comorbidity of depressive disorders and eating disorders, and they suggest some possible clinical guidelines for practitioners. Because the research on eating disorders is expanding so rapidly, the area is benefiting from this expansion in numerous ways, such as a better understanding of diversity issues in this area (e.g., Thompson-Brenner et al., 2013; also see Le, Boyd, & Lara, ch. 33).

In chapter 12, Capaldi and Kim discuss the comorbidity of depression and conduct disorder. In addition to both of these disorders being quite important and disruptive for day-to-day living, this area may be an example of high comorbidity that is not as anticipated by mental health care professionals as some of the other specific comorbidities discussed in this book. Nevertheless, the comorbidity of depressive disorder and conduct disorder is quite high. Capaldi and Kim discuss numerous features of this comorbidity, including models of shared risk and causality, the generally poorer adjustment that follows this comorbid condition versus either condition presenting alone; relevant developmental and gender issues; certain distinctions in the findings for subthreshold disorders versus those that reach *DSM* diagnostic thresholds; and some issues for future efforts on theory, research, and practice. The authors also discuss clinical implications regarding assessment and treatment of these comorbid disorders.

In chapter 13, Klein, Bufferd, Ro, and Clark discuss depression and comorbidity in the context of personality disorders. The authors note that there are many challenges in this area, including controversy about how to best diagnose personality disorders, conceptual challenges in terms of symptom overlap with depressive disorders, research issues in terms of methodological concerns regarding the reliability and validity of personality diagnoses, clinical challenges in terms of the relatively large number of personality disorders and the resistance of these disorders to therapeutic change, and several other challenges and quandaries. Trait-like styles of dysfunctional thinking, and similar symptoms in personality disorders, have also been investigated in the context of relapse prevention for depression (e.g., van Rijsbergen et al., 2013; also see Richards & Perri, 2010). The authors discuss some recent and ongoing research regarding studies investigating the associations between depressive symptoms, maladaptive personality traits, psychosocial functioning, and several possible diagnostic approaches. This is a complex area, and Klein and colleagues provide a helpful discussion that integrates many of the primary issues and concerns. In addition, the authors discuss further directions for research, along with some of the clinical implications regarding assessment and treatment of comorbid depressive and personality disorders.

In chapter 14, Feldman and Larsen discuss the comorbidity of depression and sexual dysfunction. The authors include a discussion of some information about sexual dysfunctions per se in both men and women. In addition, the authors bring their disciplinary perspectives, with backgrounds in medicine and clinical psychology, into play as they discuss the topic of comorbid depression and sexual dysfunction. Feldman and Larsen discuss a wide range of issues regarding the interconnections between neurobiology, psychology, social issues, and depressive comorbidity with sexual dysfunctions. The authors also discuss the fluctuation of depressive comorbidity rates from one sexual dysfunction to another, along with various bidirectional causal models that may potentially explain improvement (or deterioration) in one condition following improvement (or deterioration) in the other. Finally, Feldman and Larsen include a summary of clinical implications for the evaluation and

treatment of comorbid depressive disorders and sexual dysfunctions.

In chapter 15, Cohen, Callaway, and Auster discuss the comorbidity of depression and schizophrenia. Depressive disorders frequently co-occur with schizophrenia spectrum disorders (American Psychiatric Association, 2013), and Cohen and colleagues discuss the complex—and sometimes contradictory—research literature on this topic. The authors take a broad approach to integrating the relevant literature by focusing on clinical, behavioral, cognitive, phenomenological, and neurobiological findings, which appear to be specific to the comorbidity of depression and schizophrenia. In addition, Cohen et al. discuss some of the clinical implications and treatment considerations regarding patients who exhibit comorbid depression and schizophrenia.

In chapter 16, Cukrowicz and Poindexter discuss the important clinical concerns—and the relevant research—regarding situations in which high suicide risk, and suicide attempts or completions, are associated with MDD. This topic has also received considerable attention in the media recently, in part because of the high suicide rates among returning U.S. combat veterans from the wars in Iraq and Afghanistan. Cukrowicz and Poindexter discuss a broad array of relevant issues, including prevalence, risk, and systematic treatment studies such as randomized controlled trials. The authors also summarize some clinical implications and recent treatment approaches that appear to have empirical support.

In chapter 17, Youngstrom and Van Meter discuss the comorbidity of depressive disorders and bipolar disorders. Although the diagnostic criteria for MDD is virtually unchanged between *DSM-IV* and *DSM-5* (American Psychiatric Association, 1994, 2000, 2013), the diagnostic criteria for bipolar disorders have undergone some modest revisions (in our opinion), which will have some impact on diagnostic decisions but very little on the comorbidity issues addressed in this chapter and book. Youngstrom and Van Meter discuss a wide range of relevant issues regarding comorbidity between depressive and bipolar disorders, including the long history of discussions about the association of depression and mania, epidemiological research on this comorbidity, phenomenological variables, developmental findings, family history, and relevant treatment studies. The authors note that methodological challenges in this area, along with concerns about achieving satisfactory reliability and validity in assessments, yield a database that is complicated, sometimes contradictory, and often difficult to integrate clearly. The authors also discuss some of the clinical implications, such as one disorder likely impacting the course of the other, and the implications of shared liabilities versus liabilities that appear to be more specific to depression or bipolar disorder.

Comorbidity of Depressive Disorders and Chronic Health Problems and Diseases

In chapters 18 to 27, and also to some extent in chapters 30 and 34, comorbidity between depressive disorders and specific chronic health problems (or an array of associated chronic health problems) is emphasized. For example, in chapter 18 Suls and Davidson discuss the comorbidity of depression and cardiovascular disease. One of the reasons this topic is very important is that cardiovascular disease is often listed as the number-one cause of death in industrialized countries, and the comorbidity of this disease with severe depression such as MDD is usually associated with additional complications during acute treatment, maintenance intervention, and long-term follow-up care. Suls and Davidson discuss numerous issues, including risk factors, biologically associated variables such as immune activity, and behavioral/psycho-social variables such as medical adherence and lifestyle change. The authors also discuss a complex and sometimes confusing literature regarding the impact of treatment programs for depression in patients who have cardiovascular disease. Not surprisingly, the authors note that further large-scale randomized clinical trials would help clarify this situation. Suls and Davidson also discuss some of the clinical issues and unresolved questions that may impact practitioners' decisions about how to best treat a cardiac patient with severe depression.

In chapter 19, A. Nezu, C. Nezu, Greenberg, and Salber discuss the comorbidity of depression and cancer. The authors note the recent explosion in research (and research funding) on the comorbid condition of depression and cancer. Nezu et al. discuss a number of issues in this area, including epidemiological research, risk factors, and the very negative impact that comorbid depression and cancer appears to predict for important outcome issues such as medical adherence, lifestyle enhancement, mood regulation, coping, morbidity, and mortality. As in several of the other chapters, the authors note surveys by the World Health Organization and other organizations that implicate depression as a leading cause of disability. In addition, several treatment implications are evident in the authors' discussion of these issues.

In chapter 20, Roditi, Waxenberg, and Robinson discuss the comorbidity of depressive disorders and pain. The authors note that this type of comorbidity is very common and often quite disabling. Roditi et al. discuss relevant theories, epidemiological issues, patterns of symptomatology, and implications for assessment and treatment. The authors also discuss some neurobiological variables that are important to this type of comorbidity. In addition, Roditi and colleagues summarize an array of current treatment approaches for comorbid depression and pain and discuss the evidence base of support for these approaches.

In chapter 21, Dutton and Needham discuss the comorbidity of depression and chronic obesity. With obesity (along with smoking) very high on the current lists of preventable causes of death, this topic is clearly important. The authors' discussion includes a consideration of the possible bidirectional nature of this comorbidity, where severe depression (e.g., MDD) may be a risk factor for chronic obesity and vice versa. Dutton and Needham also discuss theoretical issues, common mediating biological and environmental factors, and the available research literature for trying to untangle various hypotheses. Possible biological mediators may include dysregulation and the hypothalamic-pituitary-adrenal axis. Potential environmental and psychological mediators may include binge eating and a history of abuse. Moreover, Dutton and Needham discuss some of the complexities and cautions for making treatment recommendations in this area when the association of depression and obesity is not thoroughly understood. This is also an example of an area—and there are many in this book—where a treatment package that is multicomponent (e.g., psycho-social, medical, and lifestyle components), integrated, and multidisciplinary in nature and that targets *both* depression and the comorbid disorders or chronic health problems may be a particularly attractive treatment option (e.g., see Daumit et al., 2013, regarding obesity and mental illness; Richards, Cohen, Morrell, Watson, & Low, 2013, regarding smoking, depression, and anxiety; Rose & Behm, 2013, regarding smoking and associated mood disorders; and Wetherell et al., 2013, regarding GAD, MDD, and older-adult status).

In chapter 22, Carney and Moss discuss the comorbidity of depression and sleep disorders. This is an important area that has benefited from a dramatic increase in research during the past 25 years. Advances in technology and increases in research funding have facilitated an expanded research portfolio on comorbid depressive and sleep disorders. Carney and Moss discuss the comorbidity of depression with several sleep disorders, including hypersomnia, breathing-related sleep disturbances, and chronic insomnia. The authors indicate that there is the most empirical support for bidirectional relationships between depression and sleep disorders. Carney and Moss discuss the intricate clinical issues that should be unraveled for effective assessment and treatment, given that a number of symptoms overlap in the two groups of disorders and that approximately 90% of patients with MDD report some kind of sleep problem. Carney and Moss also argue for an integrated, multicomponent approach to treatment, which includes interventions for both disorders.

In chapter 23, Hancock, Bruce, and Lynch discuss the comorbidity of depressive disorders and multiple sclerosis (MS). Hancock et al. note that depressive comorbidity is common in MS, with about 50% of MS patients receiving a diagnosis of MDD during their lifetime. If the depression is left untreated, suicidal risk climbs and a variety of MS symptoms tend to worsen. The authors discuss some of the challenges for clinicians who are working with depressed MS patients, including the difficulty of distinguishing the symptoms of depression from the neurological symptoms and behavioral consequences of MS. In addition, Hancock and colleagues provide some clinical guidelines and considerations for the assessment, diagnosis, evaluation, treatment, and follow-up of depressed MS patients.

In chapter 24, Blashill, Gordon, Mimiaga, and Safren discuss the comorbidity of depressive disorders and HIV-positive status/AIDS. Blashill and colleagues discuss a wide range of relevant issues, including epidemiological studies; comorbidity of HIV+/AIDS with depressive and substance-use disorders; implications of depressive comorbidity for poor medical adherence, ineffective self-care, and unsafe sexual practices; and an array of associated biological and psycho-social variables. As with many of the chapters in this section of the book on comorbidity with chronic health problems, Blashill and colleagues argue for multicomponent, integrative treatments that target both the medical and psycho-social aspects of people who are living with HIV+/AIDS. In addition, the authors provide a brief overview of the literature on evidence-based interventions with a focus on improving self-care behaviors and medical adherence. The authors also discuss important directions for future research.

In chapter 25, Christensen, Van Liew, and Kellerman discuss the comorbidity of depression with chronic kidney disease. The authors discuss the negative implications of this comorbidity, such as poorer quality of life, reduced medical adherence, and higher morbidity and mortality for depressed kidney disease patients. As with most of the depression and chronic health problem comorbidities, the challenges for clinicians include unraveling the overlap in symptoms between depression and kidney disease. Unfortunately, there is not a large database of sophisticated randomized controlled trials investigating the effectiveness of integrative treatments for depressed kidney disease patients; thus Christensen and colleagues discuss some promising future directions for treatment research. The available treatment literature and clinical experience have yielded some helpful clinical guidelines, however, and Christensen and colleagues discuss these clinical recommendations for assessing and treating depressed kidney disease patients.

In chapter 26, Brommelhoff discusses the comorbidity of depressive disorders and dementia syndromes. Depressive disorders are commonly associated with many of the dementia syndromes and neurocognitive disorders (American Psychiatric Association, 2013). Brommelhoff discusses a number of the important aspects of this comorbidity, including theory, directional and bidirectional models of causation, and neurobiological and neuropsychological variables such as cerebrovascular risk factors and negative emotional reactions to cognitive decline. There is considerable overlap between symptoms of depression and symptoms of dementia syndromes (and certain examples of the other neurocognitive disorders). Brommelhoff notes that this overlap in symptoms complicates the clinician's task of assessment and evaluation, of course, but that nevertheless the differential diagnoses between depressive disorders and dementia syndromes are essential. Brommelhoff discusses some of the clinical implications and guidelines for practitioners working with depressed dementia patients. The author also includes a discussion of the possible contraindications for antidepressant medications (given the possibility of adverse reactions or negative drug interactions) and the potential effectiveness of certain psycho-social interventions.

In chapter 27, Buttner and O'Hara discuss the comorbidity of depression with three of the more common health problems regarding women's health: type 2 diabetes, fibromyalgia, and rheumatoid arthritis. The authors discuss these three chronic medical conditions regarding women's health and depression in part because the conditions are more frequently comorbid with depression in women than in men. Buttner and O'Hara consider a wide range of relevant issues, including epidemiological research; specific features of the medical conditions with particular attention to symptoms that overlap with depression; theoretical approaches to explaining the high comorbidity of these medical conditions with depression; future research directions; and clinical guidelines for assessing and treating depression in the context of type 2 diabetes, fibromyalgia, and rheumatoid arthritis in women. One of the interesting features of this chapter is that the authors address three different chronic health problems and the comorbidity with depressive disorders, rather than focusing on one health problem as most of the other chapters on comorbidity with health do.

Chapters 30 and 34 also discuss the comorbidity of depression with a health issue. In chapter 30, Felder, Lindemann, and Dimidjian discuss the topic of perinatal depression. The authors' discussion includes an evaluation of the epidemiological research, etiological theories, risk factors, specific assessment and treatment challenges, and potential negative consequences for women and offspring when a woman is pregnant and depressed or postpartum and depressed. This is another area where important research has increased during the past 25 years, and the authors discuss this research and future research directions. There are a number of promising treatment interventions in this area, from evidence-based psychotherapy (e.g., Nylen et al., 2010) to enhanced child-care services (e.g., Herba et al., 2013) for depressed pregnant and postpartum women. Felder et al. conclude the chapter with a discussion of clinical guidelines for practitioners regarding the assessment and treatment of depression during the perinatal period in women.

In chapter 34, Hopko, McIndoo, Gawrysiak, and Grassetti discuss psycho-social interventions for depressed breast cancer patients. Thus this chapter overlaps with both the "health chapters" and the "treatment chapters" in the book. Hopko and colleagues review an array of recent studies on epidemiology, theories—especially bidirectional theories—negative impacts and consequences of the comorbidity of depression and cancer, assessment and treatment approaches in the complex situation of comorbid depression and cancer, various directions for future theory and research, and treatment outcome studies involving psychosocial

interventions for depressed breast cancer patients. The authors acknowledge that many of these studies, including some of the major randomized controlled trials, have methodological and practical limitations, and therefore the authors point to future directions for stronger research. In addition, Hopko and colleagues discuss clinical guidelines for the psycho-social treatment of depressed breast cancer patients.

Comorbidity Between Depression and Relationship Distress and Dysfunction

Depression is often associated with distressed relationships, and distressed relationships are often associated with depression. This type of "depressive comorbidity" is not as classically considered in the research literature as is the depressive comorbidity with other psychiatric disorders or with chronic health problems. But this type of depressive comorbidity is very important—almost everyone cares about close relationships. Moreover, the research literature on the comorbidity of depression and relationship distress has grown exponentially in the past 30 years, just as the associated literature on close relationship issues, in general, has grown very rapidly. In chapters 28 and 29, the contributing authors address some of the issues and research regarding the comorbidity of depression and dysfunctional relationships.

In chapter 28, Stroud, Feinstein, Bhatia, Hershenberg, and Davila discuss depression in the context of intimate relationships. The authors begin their chapter by providing an overview of several of the issues and noting that concurrent and longitudinal research has thoroughly established an association between depression and relationship dysfunction. Stroud and colleagues discuss theory and conclude that bidirectional and transactional theories are the most supported. The authors go on to discuss how the specific components and processes of intimate relationships may be influenced by depression. Stroud and colleagues include a discussion of research on adolescent intimate relationships and how romantic and sexual experiences during the developmental interval of adolescence may relate to depression and vice versa. In addition, the authors discuss clinical implications for counselors and other practitioners, with a focus on cognitive-behavioral couple therapy, which appears to have some of the stronger evidence-based support.

In chapter 29, Abaied and Rudolph discuss the comorbidity of depression and family relationships—particularly disrupted family relationships. The authors' discussion includes an emphasis on emotional processes, parent–child relationships, and adolescent depression. This topic is another example of a subarea in depressive comorbidity research that has enjoyed large-scale growth in recent years. Abaied and Rudolph discuss the complex bidirectional models that appear to be best supported by empirical research and that help explain the associations and interactions between depression, family adversity, parent–child relationships, parenting behavior, and adolescent depression. The authors also offer an integrative framework for conceptualizing "emotional functioning" as one of the important mechanisms influencing how family relationships and adolescent depression influence one another over a period of time. We expect research on the comorbidity of depression and relationship dysfunction—including intimate and family relationships—to continue to grow and prosper in the foreseeable future.

Treatment of Depression and Comorbid Disorders

Chapters 31 through 35 address some aspect of the treatment of depression and comorbid disorders, with a focus on treatment issues throughout each chapter rather than a brief discussion of clinical guidelines as is the case in most of the previous chapters.

In chapter 31, Howland discusses multidisciplinary treatments and medications for depressive disorders and comorbidity. Howland's discussion includes an analysis of many of the issues regarding antidepressant medications and other psychotropic drugs, which is informed in part by the author's disciplinary perspective as a physician, psychiatrist, and psychiatric researcher. Howland covers a range of relevant topics, including comorbidity with chronic depression and treatment-resistant depression, psychiatric and medical comorbidities, adjusting for possible treatment contraindications in the cases of some medication regimens and for specific medical and psychiatric comorbidities, and the increases in disability and mortality that can be associated with depressive comorbidity. In addition, Howland—like many of the contributors to this volume—argues for multidisciplinary collaboration and integrated treatment programs that target all or most features of the comorbidity situation.

In chapter 32, Gitlin discusses the role of community and home-based interventions for cases of late-life depression; moreover, these depression cases

almost invariably involve some psychiatric, health, or relationship comorbidity. The author's discussion includes a review of 23 well-evaluated community and home-based interventions that have yielded generally positive and promising results. The benefits of such evidence-based interventions may be enormous, given the severely negative morbidity and mortality rates that may accompany comorbid depression in older adults. Gitlin notes that there are also many attractive features to community and home-based interventions for depressed older adults, including practical advantages to clients; economic advantages to providers and clients; increased access to nonpharmacologic interventions such as training in problem-solving skills, social support increases, and lifestyle enhancement; and increased access to treatment for underserved populations. Gitlin also discusses some of the intervention programs that she considers most outstanding and points to some future directions in this area regarding intervention research and practice.

In chapter 33, Le, Boyd, and Lara discuss the treatment of depressive disorders and comorbidity, particularly in the context of ethnic minority groups. This is a very important area, and ethnic minorities are often among the most underserved populations regarding interventions for comorbid depression. (This point is also made by Gitlin in chapter 32.) Le and colleagues cover a number of relevant topics, including depressive comorbidity in ethnic minority adults, treatment interventions that include some tailoring to ethnic minority populations, the challenges presented by considerable underrecognition and undertreatment of comorbid depression in ethnic minority groups in the United States, and an array of relevant needs and directions for future research and practice. The authors also discuss how culturally sensitive adaptations of evidence-based treatments for depressive comorbidity may be successfully adapted to ethnic minority groups. In addition, Le and colleagues discuss clinical guidelines for practitioners in the context of treating comorbid depression in ethnic minority groups.

In chapter 34, Hopko, McIndoo, Gawrysiak, and Grassetti discuss psychosocial interventions for depressed breast cancer patients. We discussed this chapter earlier under "Comorbidity of Depressive Disorders and Chronic Health Problems and Diseases." With the consistent emphasis on treatment issues throughout this chapter, however, the Hopko et al. chapter also fits in this section on treatment of depression and comorbid disorders. Of course many of the chapters in this book could fit nicely into more than one section. For example, chapters 2 through 5 on assessment, diagnosis, theory, and methods could also fit nicely in "The Big Picture" section below. Chapters 18 through 27 (and 30 and 34) on comorbidity of depressive disorders and chronic health problems also discuss some of the psychiatric comorbidity issues that are emphasized in chapters 6 through 17. Indeed, the topic of this book—depressive disorders and comorbidity—has a number of common issues and themes that run through most of the chapters in the book.

In chapter 35, Whisman and BE discuss cognitive therapy for comorbid depression. One of the important features of this chapter is that the authors give clinical guidelines regarding specific types of depressive comorbidity, such as the comorbidity of depression with anxiety disorders, substance-use disorders, and personality disorders. Whisman and BE discuss some of the complex issues and challenges that confront clinicians regarding the assessment, treatment, and follow-up of depressed patients with co-occurring conditions. The authors use cognitive therapy, which is one of the evidence-based therapies in this area, to illustrate some of their clinical recommendations and treatment guidelines. This chapter also echoes a theme that is evident in many of the other chapters: Comorbid depression is more difficult to treat effectively than depression by itself.

The Big Picture

Chapters 36 and 37 discuss some of the "big picture" issues regarding this book on depressive disorders and comorbidity. In chapter 36, Kessler, Scott, Shahly, and Zaslavsky discuss broad and integrative issues regarding comorbid depression. Kessler and colleagues evaluate some of the relevant epidemiological research literature, with their perspective informed by their own extensive involvement in this type of research. The authors' discussion includes an analysis of research on latent liabilities—particularly regarding the dynamics of comorbidity that involves depression and temporally primary and secondary psychiatric disorders. The authors also discuss the comorbidity of depression and chronic physical problems and diseases. Kessler and colleagues suggest that future research on depressive comorbidity would be enhanced by distinguishing between psychiatric and medical comorbidities specific to MDD, versus those that appear to reflect a broader latent liability and associations with a wider range of disorders and dysfunctions.

In chapter 37, we discuss some of the integrative themes that run through much of this book, which is usually the charge of an epilogue. As the editors, we are in a good place to note themes that seem particularly salient, important, and frequently mentioned throughout the book. Thus, for example, we note that depressive comorbidity is common and pervasive. We discuss some of the explanatory models of causation, including shared liability, overlapping symptoms, common biological factors, specific models of causal direction (e.g., unidirectional versus bidirectional), and intervention side effects that may cause or exacerbate depression. We discuss the remarkable increase in disability and disease burden (morbidity and mortality) that often accompanies comorbid depression. In part because the comorbidity rates are so very high with certain comorbidities, we take a look at a specific example: the comorbidity of depression and anxiety disorders. We discuss an array of assessment issues, which are usually more complex in cases of depression co-occurring with other disorders. We comment on the complexities and challenges that accompany intervention programs for comorbid depression. Treating depression that is comorbid with other psychiatric disorders, chronic health problems, or relationship dysfunction is very difficult—for both the practitioner and the patient (and often for significant others too). We conclude the Epilogue with some final comments on treatment issues and the seemingly ubiquitous nature of depressive comorbidity—depression goes with many other problems. The 37 chapters in this volume, *The Oxford Handbook of Depression and Comorbidity*, do an effective job in covering the extensive landscape of this important topic.

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CHAPTER

2 Diagnostic and Statistical Manual (DSM)

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Abstract

This chapter provides a discussion of the American Psychiatric Association's classification of mental disorders (DSM-I through DSM-5), with a particular emphasis on mood disorders and their classification and diagnosis. It begins with the rationale for having an official, authoritative diagnostic manual and then traces the history of the development of the first edition through the fourth edition (DSM-IV-TR, 2000). The authors then discuss fundamental issues concerning the fifth edition (DSM-5, 2013), including the definition of mental disorder, the empirical support for proposed revisions, the shift toward a dimensional model of classification, and the shift toward a neurobiologically-based classification.

Key Words: DSM-IV-TR, DSM-5, classification, diagnosis, dimensional model, neurobiologically-based classification, mental disorders, mood disorders

Diagnostic and Statistical Manual (DSM)

Persons often feel different emotions, such as happiness, passion, vulnerability, and anger. Any normal person will at times experience intense emotions, feeling strongly about some particular event or experience, either positively or negatively, and sometimes for a significant length of time. However, the mental health professions of psychiatry, clinical psychology, social work, and nursing consider the emotions or moods of some persons to represent mental disorders. What constitutes a mental disorder is largely under the authority and control of the American Psychiatric Association (and the World Health Organization [WHO]), through its *Diagnostic and Statistical Manual of Mental Disorders* (DSM), the current version of which is the DSM-IV-TR (American Psychiatric Association, 2000). As the authoritative, official nomenclature for mental disorder diagnosis, the DSM-IV-TR is in fact an exceedingly powerful document, impacting many important social, forensic, clinical, and other professional decisions (Schwartz & Wiggins, 2002). Whether or not a child receives medication, a person receives disability support, a researcher obtains a publication or receives grant funding, a patient obtains insurance coverage for treatment, or a prisoner is released from incarceration can be governed heavily by what is contained within the DSM (Frances & Widiger, 2012). In addition, persons think in terms of their language, and the predominant classifications of psychopathology in English are encompassed by the DSM-IV-TR and, in all other languages, by the tenth edition of the World Health Organization's International Classification of Diseases (ICD-10; WHO, 1992). Therefore these nomenclatures have a substantial impact on how clinicians, social agencies, students, researchers, the government, and the general public conceptualize aberrant, problematic, and maladaptive behavior.

The DSM-IV-TR is certainly informed and guided by a substantial body of empirical research (Widiger et al., 1998). However, the authority and power of the DSM-IV-TR is not necessarily

matched by its scientific foundation. The disorders included within the DSM-IV-TR are well reasoned, scientifically researched and, for the most part, well documented, representing what is currently understood by a body of scientists, theorists, researchers, and clinicians to be the predominant forms of psychopathology (Widiger, 2013). On the other hand, mental disorders are not entities that exist independent of belief systems. Mental disorders are, to a substantial extent, constructions of clinicians and researchers rather than proven, evident diseases or illnesses (Boorsboom, 2008; Meehl, 2010; Strauss & Smith, 2009). The mental disorders included within the DSM-IV-TR represent the opinions and beliefs, perhaps even just the hypotheses, of a set of psychiatrists and clinical psychologists, and much of it is subject to considerable dispute, even controversy. This chapter provides an overview of the DSM-IV-TR diagnostic nomenclature, beginning with historical background (Widiger & Crego, 2013), followed by a discussion of the major issues facing the forthcoming DSM-5, with a particular emphasis on proposals concerning disorders of mood.

Historical Background

A primary purpose of an official diagnostic nomenclature is to provide a common language for communication (Kendell, 1975; Sartorius et al., 1993). Dysfunctional, aberrant, and maladaptive ways of feeling, thinking, behaving, and relating to others are of substantial concern to many different professions, the members of which hold an equally diverse array of opinions regarding etiology, pathology, and treatment. It is imperative that these persons be able to communicate meaningfully with one another. The impetus for the development of an official diagnostic nomenclature was the chaos and confusion generated by its absence (Widiger, 2001). "For a long time confusion reigned. Every self-respecting alienist [the nineteenth-century term for a psychiatrist], and certainly every professor, had his own classification" (Kendell, 1975, p. 87). In the nineteenth century, the production of a new system for classifying psychopathology was a standard rite of passage for the young aspiring psychiatrist.

> To produce a well-ordered classification almost seems to have become the unspoken ambition of every psychiatrist of industry and promise, as it is the ambition of a good tenor to strike a high C. This classificatory ambition was so conspicuous that the composer Berlioz was prompted to remark that after their studies have been completed a rhetorician writes a tragedy and a psychiatrist a classification. (Zilboorg, 1941, p. 450)

ICD-6 and DSM-I

It was clearly untenable to have clinicians, researchers, and other mental health professionals using different diagnoses to describe and study the same psychopathology. Patients were unable to obtain consistent medical care and a scientific base of knowledge could not be accumulated.

> The present condition with respect to the classification of mental diseases is chaotic. Some states use no well-defined classification. In others the classifications used are similar in many respects but differ enough to prevent accurate comparisons. Some states have adopted a uniform system, while others leave the matter entirely to the individual hospitals. This condition of affairs discredits the science. (Salmon, Copp, May, Abbot, & Cotton, 1917, pp. 255–256)

By the time of the Second World War, the U.S. Navy, Army, and Veterans Administration had all developed their own nomenclatures. However, the Second World War was instrumental in compelling clinicians from a number of different countries to work directly with one another, bringing to immediate attention the difficulties in not having a common language. Therefore the World Health Organization (WHO) finally included a section devoted to mental disorders within the 6th edition of the International Classification of Diseases (ICD-6), published in 1948 (Kendell, 1975). The U.S. Public Health Service commissioned a committee, chaired by psychiatrist George Raines (with representatives from a variety of other professions and public health agencies) to develop a variant of the mental disorders section of ICD-6 for use within the United States. The United States, as a member of the WHO, was obliged to use ICD-6, but any particular country could make certain adjustments to maximize its acceptance and utility within its particular culture. Responsibility for publishing and distributing this committee's version of ICD-6 within the United States was given to the American Psychiatric Association (1952) under the title *Diagnostic and Statistical Manual. Mental Disorders* (hereafter referred to as DSM-I).

DSM-I was generally successful in obtaining acceptance among different clinical institutions and agencies within the United States, partly because of its expanded coverage, notably the inclusion of

somatoform disorders, stress reactions, and personality disorders, which had been of considerable interest during and after the war (Kendell, 1975). The mood disorders of DSM-I (American Psychiatric Association, 1952) included involutional psychotic reaction (characterized mostly by depression), manic-depressive reaction and psychotic depressive reaction (within the affective reactions section), depressive reaction (within the psychoneurotic disorders section), and cyclothymic personality (within the personality disorders).

At this time, though, fundamental criticisms regarding the reliability and validity of psychiatric diagnosis were also being raised (e.g., Zigler & Phillips, 1961), with some even suggesting that the concept of a mental disorder was largely a myth (e.g., Scheff, 1966; Szasz, 1960). A widely cited reliability study by Ward, Beck, Mendelson, Mock, and Erbaugh (1962) concluded that the poor reliability of mental disorder diagnosis was due largely to the inadequacies of DSM-I; specifically, its failure to provide specific, explicit guidelines as to the diagnostic criteria for each respective disorder.

The ICD-6 did not fare well internationally. The "mental disorders section [of ICD-6] failed to gain [international] acceptance and eleven years later was found to be in official use only in Finland, New Zealand, Peru, Thailand, and the United Kingdom" (Kendell, 1975, p. 91). The WHO commissioned a review by the English psychiatrist Erwin Stengel, who, in 1959, reiterated the importance of establishing an official nomenclature: "A. . . serious obstacle to progress in psychiatry is difficulty of communication. Everybody who has followed the literature and listened to discussions concerning mental illness soon discovers that psychiatrists, even those apparently sharing the same basic orientation, often do not speak the same language" (Stengel, 1959, p. 601).

Stengel (1959) attributed the failure of clinicians to accept the mental disorders section of ICD-6 to the presence of theoretical disputes, cynicism regarding psychiatric diagnosis (some theoretical perspectives opposed the use of any diagnostic terms), and the presence of abstract, highly inferential diagnostic criteria that hindered consistent, uniform applications.

ICD-8 and DSM-II

Work began on ICD-8 soon after Stengel's 1959 report (ICD-6 had been revised to ICD-7 in 1955, but there were no revisions to the mental disorders section). The text was approved by the WHO in 1966 and became effective in 1968. A companion glossary in the spirit of Stengel's recommendations was to be published conjointly, but work did not begin on the glossary until 1967 and it was not completed until 1972. "This delay greatly reduced [its] usefulness, and also [its] authority" (Kendell, 1975, p. 95). In 1965, the American Psychiatric Association appointed a committee, chaired by Ernest M. Gruenberg, to revise DSM-I to be compatible with ICD-8 and yet also be suitable for use within the United States. The final version was approved in 1967, with publication in 1968.

The diagnosis of mental disorders, however, was continuing to receive fundamental criticism (e.g., Rosenhan, 1973). A major problem was the absence of empirical support for the reliability, let alone validity, of the diagnoses (e.g., Blashfield & Draguns, 1976). Some researchers, therefore, took to heart the recommendations of Stengel (1959) to develop more specific and explicit criterion sets (Blashfield, 1984). The most influential of these initiatives was provided by a group of psychiatrists and psychologists at Washington University in St. Louis. They demonstrated that their relatively specific and explicit diagnostic criteria could obtain replicable research findings. Their criterion sets generated so much interest that they were published separately in what became one of the most widely cited papers in psychiatry (i.e., Feighner et al., 1972). As expressed recently by Kendler, Munoz, and Murphy (2010), "the renewed interest in diagnostic reliability in the early 1970s—substantially influenced by the Feighner criteria—proved to be a critical corrective and was instrumental in the renaissance of psychiatric research witnessed in the subsequent decades" (p. 141).

The Feighner et al. (1972) criterion sets were confined to just the 14 "psychiatric illnesses" and one secondary condition of primary interest to the Washington University researchers. Included therein were primary affective disorder (depression and mania) and secondary depression. Secondary depression was not considered a real "psychiatric illness," as it occurred in the context of another mental disorder or a life-threatening medical illness. Their approach to diagnosis was greatly expanded by Robert Spitzer, a technical consultant for DSM-II (American Psychiatric Association, 1968), into a manual that covered a much wider variety of disorders, titled the *Research Diagnostic Criteria* (RDC) (Spitzer, Endicott, & Robins, 1978), which was subsequently adopted by many research programs around the world.

ICD-9 and DSM-III

By the time the work of Feighner et al. (1972) was published, work was nearing completion on ICD-9. The authors of ICD-9 had decided to include a supplementary glossary in the spirit of Stengel (1959) to facilitate reliable diagnosis, but it was apparent that they would not include the more specific and explicit criterion sets developed and used in research settings (Kendell, 1975). Robert Spitzer was appointed to chair the revision of DSM-II in a manner that would be compatible with ICD-9 but also incorporate many of the advances in diagnosis currently being developed. DSM-III was published in 1980 and was remarkably innovative, including (1) a multiaxial diagnostic system (most mental disorders were diagnosed on Axis I, personality and specific developmental disorders were diagnosed on Axis II, medical disorders on Axis III, psychosocial stressors on Axis IV, and level of functioning on Axis V), (2) specific and explicit criterion sets for all but one of the disorders (i.e., schizoaffective), (3) a substantially expanded text to facilitate diagnosis (e.g., age of onset, sex ratio, course, and familial pattern), and (4) removal of terms (e.g., *neurosis*) that appeared to favor a particular theoretical model (American Psychiatric Association, 1980; Spitzer, Endicott, & Robins, 1975; Spitzer, Williams, & Skodol, 1980).

DSM-III-R

Many of the criterion sets developed for DSM-III lacked much prior research or field testing. Most were constructed by work group members with little guidance as to how they would actually perform in general clinical practice or even research settings. As a result, a number of obvious errors occurred (e.g., panic disorder in DSM-III could not be diagnosed in the presence of major depression). "Criteria were not entirely clear, were inconsistent across categories, or were even contradictory" (American Psychiatric Association, 1987, p. xvii). The American Psychiatric Association therefore authorized the development of a revision to DSM-III to make corrections and refinements. Fundamental revisions were to be tabled until work began on ICD-10.

However, it might have been unrealistic to expect the authors of DSM-III-R to confine their efforts to refinement and clarification, given the impact and acclaim of DSM-III (Blashfield, 1984; Klerman, 1986). Prior to DSM-III few psychiatrists or psychologists were particularly interested in diagnosis and classification. Subsequent to DSM-III, psychiatric diagnosis became a major focus of scientific investigation. It was not difficult to find persons who wanted to be involved in the development of DSM-III-R, and everyone who was involved (and many more who were not) wanted to have a significant impact. Ironically, there were considerably more persons working on DSM-III-R than had worked on DSM-III, yet its stated mission was far more conservative. Not surprisingly, in the end there were many proposals for major revisions and even new diagnoses, some of which proved to be highly controversial. Four of the diagnoses approved for inclusion by Spitzer and the DSM-III-R central committee (i.e., late luteal phase dysphoric disorder [the name for which was subsequently changed to premenstrual dysphoric disorder], self-defeating personality disorder, sadistic personality disorder, and paraphiliac rapism) were vetoed by the Board of Trustees of the American Psychiatric Association. A concern common to all of them was that their inclusion might result in significant negative social consequences, to women in particular. For example, premenstrual dysphoric disorder could contribute to a considerable amount of stigmatization with respect to normal premenstrual dysphoria, as well as potentially excessive and/or unnecessary pharmacotherapy. A related concern was the lack of sufficient empirical support to address or offset the concerns regarding potential harm and misusage. A compromise was eventually reached in which late luteal phase dysphoric disorder (Endicott, 2000) and the two personality disorders were included in an appendix; paraphiliac rapism was deleted entirely.

ICD-10 and DSM-IV

Work on DSM-III-R was supposed to have been completed in 1985, but given the ever-expanding breadth of its new additions and revisions, by the time work was completed on DSM-III-R work had already begun on ICD-10. The decision of the authors of DSM-III to develop an alternative to ICD-9 (i.e., include specific and explicit criterion sets) was instrumental in developing a highly innovative and internationally popular manual (Kendell, 1991; Spitzer et al., 1980). However, its innovations also came at the cost of decreasing compatibility with the ICD-9 nomenclature, used throughout much of the rest of the world, which is problematic to the stated purpose of providing a common language of communication. In 1988 the American Psychiatric Association appointed the DSM-IV Task Force chaired by Allen Frances (Frances, Widiger,

& Pincus, 1989). Mandates for DSM-IV included better coordination with ICD-10 and improved documentation of empirical support.

The DSM-IV committee aspired to use a more conservative threshold for the inclusion of new diagnoses and to have decisions be governed more openly and explicitly by the scientific literature (Frances et al., 1989). Proposals for additions, deletions, or revisions were guided by literature reviews, which were required to use a specific meta-analysis format that maximized the potential for informative critical review, containing (for example) a method section that documented explicitly the criteria for including and excluding studies and the process by which the literature had been reviewed (Widiger & Trull, 1993). The purpose of this structure was to make it easier to discover whether the author was confining his or her review only to studies that were consistent with a particular proposal and failing to acknowledge opposing perspectives. It was not unusual in the development of DSM-IV to find that proponents of a proposed revision attempted to limit their review largely to the studies that supported their proposal, neglecting to acknowledge issues and findings inconsistent with their position (Frances & Widiger, 2012; Widiger & Trull, 1993). The literature reviews were distributed for critical review, many were submitted to journals for peer review, and all were published within the three-volume *DSM-IV Sourcebook* (e.g., Widiger et al., 1994).

Testable questions that could be addressed with existing datasets were also explored in additional studies, which emphasized the aggregation of multiple datasets from independent researchers, preferably with opposing theoretical perspectives (Widiger & Trull, 1993). In addition, 12 field trials were conducted to provide reliability and validity data on proposed revisions. The primary purposes of the field trials were to address fundamental questions or concerns with regard to a particular proposal, test alternative proposals, and compare and contrast the proposals to the existing DSM-III-R (American Psychiatric Association, 1987), often with respect to external validators. The results of the field trials were published in the fourth volume of the *DSM-IV Sourcebook* (Widiger et al., 1998). Critical reviews of these additional projects were obtained by sending initial drafts to advisers or consultants for a respective work group, by presenting drafts at relevant conferences, and by submitting reports to peer-reviewed journals (Widiger, Frances, Pincus, Davis, & First, 1991; Widiger & Trull, 1993).

DSM-IV-TR

One of the innovations of DSM-III was the inclusion of a relatively detailed text discussion of each disorder, including information on age of onset, course, gender, and familial pattern (Spitzer et al., 1980). This text was expanded in DSM-IV to include culture and ethnicity, life-span development, and laboratory and physical exam findings (American Psychiatric Association, 1994; Frances, First, & Pincus, 1995). Largely excluded from the text was information concerning etiology, pathology, and treatment, as this material was considered to be too theoretically specific and more suitable for academic texts. Nevertheless, it had also become apparent that DSM-IV was being used in some settings as a textbook, and the material on age, course, prevalence, and family history was quickly becoming outdated as new information was being gathered.

Therefore, in 1997, the American Psychiatric Association appointed the DSM-IV Text Revision Work Group, chaired by Michael First (editor of the text and criterion sets for DSM-IV) and Harold Pincus (vice-chair for DSM-IV) to update the text material. No substantive changes in the criterion sets were to be considered, nor were any new additions, subtypes, deletions, or other changes in the status of any diagnoses to be implemented. In addition, each of the proposed revisions to the text had to be supported by a systematic literature review critiqued by multiple advisors. The DSM-IV Text Revision (DSM-IV-TR) was published in 2000 (American Psychiatric Association, 2000).

The outcome, however, was not entirely consistent with the original intentions. Although it was stated in the introduction to DSM-IV-TR that "no substantive changes in the criteria sets were considered" (American Psychiatric Association, 2000, p. xxix), substantive revisions were in fact made to the criterion sets for tic disorders and for the paraphilias involving a nonconsenting victim (First & Pincus, 2002), the latter owing to concerns of misapplication within forensic settings (First & Halon, 2008; Frances, 2010). In addition, no documentation of the scientific support for the text revisions was ever provided owing to the inconsistency in the quality of the effort. Some authors provided excellent documentation; however, others confined their citations largely to their own work and still others provided grossly inadequate to no documentation at all. Rather than have inconsistent and/or inadequate documentation, it was decided to have none at all.

Issues for DSM-5

Work is now well under way for DSM-5, chaired by Drs. David Kupfer and Darrel Regier, with an anticipated publication date of 2013. DSM-5 is likely to include a number of major revisions. The proposals were posted online February 10, 2010, and subsequently revised in January 2011; June 2011; and April 2012 (see www.dsm5.org). The content and process of DSM-5 has been controversial (Frances, 2009). Four issues discussed here are (1) the definition of mental disorder, (2) the empirical support for proposed revisions, (3) shifting to a dimensional model, and (4) shifting to a neurobiological model (Widiger & Crego, 2013).

Definition of Mental Disorder

A fundamental concern of the diagnostic manual is what constitutes a mental disorder. The boundaries of the DSM have been increasing with each edition (Kirk, 2005) and there has long been vocal concern that much of this expansion represents an encroachment into normal problems of living (Caplan, 1995; Folette & Houts, 1996; Maddux, Gosselin, & Winstead, 2008). The authors of DSM-5 have been proposing quite a few new diagnoses, such as paraphilic coercive disorder, hypersexual disorder, olfactory reference syndrome, hoarding, skin picking disorder, pedohebephilia, disinhibited social engagement disorder, nonsuicidal self-injury, behavioral addiction, minor neurocognitive disorder, attenuated psychosis syndrome, and binge eating disorder. Of particular relevance to mood disorder researchers and clinicians would be the proposals for disruptive mood dysregulation disorder (previously titled temper dysregulation of childhood), mixed anxiety-depressive disorder, and premenstrual dysphoric disorder. There is also a proposal to remove or modify the bereavement exclusion criterion for major depressive disorder as well as to include a new diagnosis of persistent complex bereavement disorder.

Ideally one should be able to determine what is or is not a mental disorder based upon an explicit definition of what constitutes a mental disorder. The definition of mental disorder provided in DSM-IV-TR (American Psychiatric Association, 2000) was the result of an effort by the authors of DSM-III to develop specific and explicit criteria to be used for deciding whether a behavior pattern (homosexuality in particular) should be classified as a mental disorder (Spitzer & Williams, 1982). The primary features of the definition of mental disorder included in DSM-IV-TR are occurrence within the individual (i.e., DSM-IV-TR does not include relationship disorders); the behavior or syndrome is associated with clinically significant distress, disability, impairment, and/or loss of freedom; the behavior or syndrome is not an expectable and culturally sanctioned response to a particular event (such as the death of a loved one); and the behavior or syndrome is not simply a culturally deviant or denounced behavior (e.g., political, religious, or sexual) that places the person in conflict with society (American Psychiatric Association, 2000). Contributing to the decision that homosexuality was not a mental disorder was the conclusion that the distress and impairment experienced by persons receiving the diagnosis were due largely to formal and informal condemnation of homosexuality by a significant proportion of society (Spitzer, 1981).

The intense controversy that surrounded the inclusion of homosexuality within prior editions of the diagnostic manual has largely abated, but the issues raised in reference to the definition of mental disorder continue to fester. Consider, for example, major depressive disorder and bereavement. Currently, clinicians are discouraged from diagnosing persons with a mood disorder if the depression is in response to the loss of a loved one and has lasted less than two months (American Psychiatric Association, 2000). Two months is, of course, a rather arbitrary point of demarcation between normal and abnormal grieving but, most importantly, the exclusion criterion is clearly an effort of the American Psychiatric Association to avoid pathologizing what is considered by most persons within society to be a normal, natural response to the loss of a loved one (Horwitz & Wakefield, 2007). Wakefield and colleagues have argued, however, that it is also arbitrary to single out the loss of a loved one with such unique importance (e.g., Wakefield, Schmitz, First, & Horwitz, 2007). Persons also become understandably depressed in response, for instance, to the loss of employment, marital dissolution, or a life-threatening physical illness. Wakefield et al., therefore, have suggested expanding the exclusion criterion to include these (and other) additional losses.

The DSM-5 Mood Disorders Work Group, however, did not embrace Wakefield's argument. On the contrary, they proposed to eliminate the bereavement exclusion criterion in part because it is illogical and inconsistent to distinguish the loss of a loved one from other comparable stressors, such as rape, betrayal by a spouse, or developing cancer (Kendler, 2010). A removal of the bereavement

exclusion criterion would be explicitly inconsistent with the DSM-IV-TR definition of mental disorder stating that the "syndrome or pattern must not be merely an expectable and culturally sanctioned response to a particular event, for example, the death of a loved one" (American Psychiatric Association, 2000, p. xxxi) as well as the proposed definition for DSM-5, which continues, so far, to state that an expectable response to the loss of a loved one would not be a mental disorder (Stein et al., 2010). However, the DSM-5 definition of mental disorder would likely be revised to be consistent with the Mood Disorders Work Group decision if the latter committee decides to remove this exclusion criterion.

Research has questioned whether there is any real distinction between a depressive response to the loss of a loved one and a depressive response to some other type of loss (e.g., Kendler, Myers, & Zisook, 2008; Wakefield et al., 2007; Zisook & Kendler, 2007), nor does there appear to be a meaningful difference between depression secondary to bereavement and major depressive disorder independent of bereavement (Lamb, Pies, & Zisook, 2010) other than perhaps simply the severity of the mood (e.g., Wakefield et al., 2007). First (2011) and Wakefield (2011; Wakefield & First, 2012) argue that removal of the exclusion criterion will likely contribute to a considerable amount of pathologizing what is largely a normal human response (Horwitz & Wakefield, 2007). However, the fact that the depression is an expectable response to the loss of a loved one might not negate the occurrence of a disorder any more than it does in response to any other loss or stressor. Instead, it could be providing a partial but necessary explanation for the etiology of the disorder, just as it does for other losses (Widiger, 2013). It is natural and normal to develop the flu in response to contact with a virus or to die in response to a severe trauma to the head. Because the response is natural and expected does not imply or suggest that the response is healthy or should not be considered a disorder. It is true that in many instances of a depressive reaction in response to the loss of a loved one the depression resolves without professional intervention (Wakefield & First, 2012), but this is also true for many minor physical illnesses and injuries. The fact that medical treatment is not required for the depression to remit does not imply or suggest that a disorder did not in fact occur.

Nevertheless, the DSM-5 proposal that depression in response to the death of a loved one is a mental illness received considerable criticism and objection. The DSM-5 Mood Disorders Work Group therefore modified the proposal somewhat. They acknowledged that a normal and expected response to a significant loss (e.g., bereavement, as well as financial ruin or natural disaster) will include feelings of intense sadness, rumination, insomnia, poor appetite, and weight loss and therefore could resemble an actual mood disorder. When these symptoms reach the level of feelings of worthlessness, suicidal ideation, psychomotor retardation, and severe impairment, they would be considered to be a mood disorder even if they are in response to the loss of a loved one (or in response to any other loss). Proposed for an appendix to the DSM-5 (for disorders requiring further research) would be a diagnosis of "persistent complex bereavement disorder" that involves a preoccupation with the loss of the loved one for more than 12 months (for children only 6 months).

Wakefield (1992) developed an alternative "harmful dysfunction" definition of mental disorder wherein dysfunction is a failure of an internal mechanism to perform a naturally selected function (e.g., the capacity to experience feelings of guilt in a person with antisocial personality disorder) and harm is a value judgment that the design failure is harmful to the individual (e.g., failure to learn from mistakes results in repeated punishments, arrests, loss of employment, and eventual impoverishment). Wakefield's definition has received substantial attention and was being considered for inclusion in DSM-5 (Rounsaville et al., 2002). However, his proposal has also received quite a bit of critical review (e.g., Bergner, 1997; Kirmayer & Young, 1999; Lilienfield & Marino, 1999; Widiger & Sankis, 2000) and is no longer under serious consideration (Stein et al., 2010).

Missing from Wakefield's (1992) definition of mental disorder and the DSM-IV-TR is any reference to dyscontrol (unless one stretches the concept of the loss of freedom included within the DSM-IV-TR definition of mental disorder to include most forms of dyscontrol). Mental disorders are perhaps best understood as dyscontrolled impairments in psychological functioning (Kirmayer & Young, 1999; Klein, 1999; Widiger & Trull, 1991). "Involuntary impairment remains the key inference" (Klein, 1999, p. 424). Dyscontrol is a fundamental component within Bergner's (1997) "significant restriction" and Widiger and Sankis's (2000) "dyscontrolled maladaptivity" definitions of mental disorder. Dyscontrol might even provide a basis for a fundamental distinction between mental

and physical disorder, as dyscontrol is not a meaningful consideration for a physical disorder.

It is perhaps the inability or difficulty to alter or adjust problematic feelings, thoughts, or behaviors that suggests the presence of a mental disorder. To the extent that persons willfully, intentionally, freely, or voluntarily engage in harmful sexual acts, gambling, drug usage, or child abuse, they would not be considered to have a mental disorder. Persons seek professional intervention in large part to obtain the insights, techniques, skills, or other tools (e.g., medications) that help increase their ability to better control and manage their mood, thoughts, or behavior. Of course, if a mental disorder is present when there is both dyscontrol and impairment, then depression in response to the loss of a loved one would be classified as a mental disorder to the extent that the person was unable to control his or her feelings of depression and these depressive feelings were resulting in significant social, personal, or occupational impairment.

Empirical Support

In the absence of a clear consensus as to what constitutes a mental disorder, the lack of any gold standard for any particular diagnosis, and the presence of considerable dispute and debate within the field regarding the validity of respective mental disorder diagnoses, one might anticipate that decisions for major revisions would be supported by a substantial body of empirical evidence. Proposals for DSM-III-R were rejected by the American Psychiatric Association's Board of Trustees because there was inadequate research to address concerns with respect to possible risks and costs (Endicott, 2000). A mandate given to the authors of DSM-IV was to be more cautious and to provide better documentation for the decisions that were made (Frances et al., 1989).

DSM Work Group members are typically specialists within a particular area of diagnosis and classification. Such experts are necessary, but they tend to be focused primarily on the perceived failure of the diagnostic manual to provide adequate coverage (Frances & Widiger, 2012). Their primary and at times perhaps sole concern is with the potential false negatives—the missed diagnosis or the patient who does not fit within an existing diagnosis. They tend to be relatively disinterested in the false positives: patients who receive unnecessary diagnosis, treatment, or stigma and consequently must bear unnecessary expense. Experts also tend to be very confident about their positions, having developed through their research empirical support for a proposed diagnosis, accompanied by relatively little familiarity or even interest in how the diagnosis might be misapplied within routine clinical practice, the potential impact of drug company marketing, health economics, forensic misuse, and the many other social-clinical impacts of a DSM.

Frances, the chair of DSM-IV, had suggested that "the major innovation of DSM-IV will not be in its having surprising new content but rather will reside in the systematic and explicit method by which DSM-IV will be constructed and documented" (Frances et al., 1989, p. 375). Frances (2009) has suggested more recently that the authors of DSM-5 may have flipped this priority on its head, with emphasis being given to surprising new content and inadequate attention to first conduct systematic, thorough, and balanced reviews to ensure that the proposals have adequate justification and empirical support and that the potential costs and risks of the proposed diagnosis have also been addressed. It is perhaps ironic that a drug company cannot release a medicine into clinical practice without first addressing, empirically, the potential costs and risks of the medicine along with its purported benefits, yet there is no comparable control over the release of new diagnoses that will likely be treated with a variety of potentially harmful medications. Concerns with respect to the process with which DSM-5 was being constructed were perhaps first raised by Robert Spitzer, Chair of DSM-III and DSM-III-R, after having been denied access to the minutes of DSM-5 Work Group meetings (Decker, 2010). Frances and Spitzer eventually submitted a joint letter to the American Psychiatric Association's Board of Trustees on July 7, 2009, expressing a variety of concerns with respect to the process with which DSM-5 was being constructed.

The chair and vice-chair of DSM-5 have stated that the development of DSM-5 is following the procedure used for DSM-IV, including literature reviews, data reanalyses, and field trials (Regier, Narrow, Kuhl, & Kupfer, 2009). Kendler, Kupfer, Narrow, Phillips, and Fawcett (2009) developed guidelines for DSM-5 work group members indicating that any change to the manual should be accompanied by "a discussion of possible unintended negative effects of this proposed change, if it is made, and a consideration of arguments against making this change should also be included" (p. 2). Kendler et al. further stated that "the larger and more significant the change, the stronger should be the required level of [empirical] support" (p. 2).

Some of the DSM-5 literature reviews posted on the DSM-5 website do appear to meet the spirit of the Kendler et al.'s guidelines (e.g., see the review for hypersexual disorder; www.dsm5.org). However, others perhaps not so much (e.g., see the reviews for mixed-anxiety depressive disorder and premenstrual dysphoric disorder; www.dsm5.org).

The letter by Frances and Spitzer was initiated because the field trials for DSM-5 were about to begin before the proposals had received any critical or external review. Their letter was perhaps instrumental in the delay of the field trial, allowing time for the proposals to be posted on a website for public review (Decker, 2010). Some of the proposals have since been curtailed or significantly modified in response to the external critiques, but concerns about the process do still remain. For example, in a step back from the field trials that were conducted for DSM-IV, the DSM-5 field trials do not necessarily include the DSM-IV-TR criterion sets or external validators, and will therefore in many instances be unable to provide information concerning a shift in the prevalence, reliability, or validity of the diagnostic manual resulting from proposed revisions.

The threshold for the inclusion of a new diagnosis within the DSM has varied across each edition. For DSM-III, Spitzer and colleagues indicated that the threshold for inclusion was fairly liberal:

> Because the DSM-III classification is intended for the entire profession, and because our current knowledge about mental disorder is so limited, the Task Force has chosen to be inclusive rather than exclusive. In practice, this means that whenever a clinical condition can be described with clarity and relative distinctness, it is considered for inclusion. If there is general agreement among clinicians, who would be expected to encounter the condition, that there are a significant number of patients who have it and that its identification is important in their clinical work, it is included in the classification. (Spitzer, Sheehy, & Endicott, 1977, p. 3)

This liberal threshold, though, led to a number of controversial proposals for DSM-III-R (e.g., premenstrual dysphoric disorder) that were, as noted earlier, vetoed by the American Psychiatric Association's Board of Trustees. The threshold for inclusion in DSM-IV was considerably more conservative (Frances et al., 1989), in a spirit of "holding the line on proliferation" (Pincus, Frances, Davis, First, & Widiger, 1992, p. 112). Specifically, it was indicated that DSM-IV would be informed and guided by research; its purpose was not to generate or stimulate research. The same spirit would seem to be present for DSM-5, as the official guidelines state that a new diagnosis should have "support from several high priority validators" and "should rarely if ever be based solely on reports from a single researcher or research team" (Kendler et al., 2009, p. 5). However, Regier, the vice chair of DSM-5, acknowledged in an interview with *Medscape Today* that some of the proposals "are not as well studied as others and we recognize that, but we can't move forward without some of these put into practice" (Brauser [interviewer] and Regier [interviewee], 2011). He noted that it is difficult to get researchers to study disorders that are not included within the diagnostic manual and indicated that a purpose of the DSM-5 will be to generate the research necessary for the validation of the proposal. "That's what the DSM is—a set of scientific hypotheses that are intended to be tested and disproved if the evidence isn't found to support them" (Brauer [interviewer] and Regier [interviewee], 2011). This perspective, however, may be shortsighted, failing to consider the clinical implications of including new, lesser-researched diagnoses. An alternative perspective is that the DSM is a manual used by clinicians and various social and forensic agencies to identify what the American Psychiatric Association has determined are sufficiently well-validated disorders to warrant official recognition.

This tension between the liberal inclusive approach and a more conservative restrictive approach is evident with respect to the proposal to include in DSM-5 mood dysregulation disorder (previously temper dysregulation disorder with dysphoria), a disorder involving outbursts of anger and rage with an onset prior to age 10. The impetus for the proposal is the marked increase in the rate at which children are being diagnosed with bipolar mood disorder in the absence of adequate scientific support for the validity of this diagnosis in children (Blader & Carlson, 2007; Fawcett, 2010; Moreno et al., 2007). As acknowledged by the DSM-5 Childhood and Adolescent Disorders Work Group (2010), "the work has been done predominately by one research group in a select research setting, and many questions remain unanswered" (p. 4). This point is reiterated within a joint statement by the DSM-5 Mood Disorders and Childhood and Adolescent Disorders Work Groups (2010) that "both work groups are concerned by the fact that the work on severe mood dysregulation [in children] has been done predominately by one research group in a select research setting" (p. 6). Nevertheless, it is

felt that problematic overdiagnosis in clinical practice could be addressed through the development of specific and explicit diagnostic criteria that might be sufficiently restrictive in its coverage. Of course, the existence of the diagnosis within the manual may also lend the condition a considerable degree of credibility and perceived validity that it does not really deserve (Hyman, 2010). The authors of the proposal suggest that its inclusion will generate the research needed for its validation. "Indeed, it can be argued that one of the major 'take-home' messages from the controversy about the diagnosis of pediatric bipolar disorder is the fact that the research needs of a large population of children with severe irritability are not being met, particularly with respect to clinical trials" (DSM-5 Mood Disorders and Childhood and Adolescent Disorders Work Groups, 2010, p. 8). As expressed by the DSM-5 Childhood and Adolescent Disorders Work Group (2010), the inclusion of this new diagnosis will help to " 'jump-start' research on severe irritability in youth" (p. 9).

Shifting to a Dimensional Model of Classification?

"DSM-IV-TR is a categorical classification that divides mental disorders into types based on criterion sets with defining features" (American Psychiatric Association, 2000, p. xxxi). This categorical classification is consistent with the medical tradition in which it is believed (and often confirmed in other areas of medicine) that each disorder has a unique and quite specific etiology, pathology, and treatment (Zachar & Kendler, 2007). The intention of the diagnostic manual is to help the clinician determine which particular disorder is present, the diagnosis of which would indicate the presence of a distinct pathology that would explain the occurrence of the symptoms and suggest a specific treatment that would ameliorate the patient's suffering (Frances et al., 1995; Kendell, 1975).

It is evident, however, that DSM-IV-TR routinely fails in guiding a clinician to the identification of one specific disorder. Despite the best efforts of the authors of each revision to the diagnostic manual to revise the criterion sets to increase their specificity, multiple diagnoses are common (Craddock & Owen, 2005; Kendell & Jablensky, 2003; Widiger & Clark, 2000; Widiger & Gore, 2012). Diagnostic comorbidity, a primary focus of this text, is perhaps the norm rather than the exception (Krueger & Markon, 2006).

The term *comorbidity* refers to the co-occurrence of distinct disorders, impacting the course or treatment of one or another, each presumably with its own etiology and pathology (Feinstein, 1970). There are indeed many instances in which the presence of multiple diagnoses suggests the presence of distinct yet comorbid psychopathologies. There is clearly a substantial body of research on the many disorders and conditions with which depression is comorbid, including substance use disorders, schizophrenia, sexual dysfunctions, coronary heart disease, cancer, diabetes, and many, many more covered within this book. The high prevalence of diagnostic comorbidity throughout the diagnostic manual was itself the primary focus of the National Comorbidity Survey (NCS), a congressionally mandated study designed to identify extent of mental disorder comorbidity within an extensive (N = 8,098) and representative sample of the United States, aged 15 to 54. Kessler et al. (1994) reported on the basis of this study that the most common lifetime disorder was major depression (17%) and that the vast majority of the lifetime disorders were comorbid (i.e., 79%). They concluded that "the major burden of psychiatric disorder. . . is concentrated in a group of highly comorbid people" (p. 11). A replication of the NCS was subsequently conducted (N = 9,090) in a face-to-face survey from 2001 to 2002 using DSM-IV criterion sets (Kessler, Berglund et al., 2003). They reported a lifetime prevalence rate of 16.2% for major depressive disorder, with 72% of these persons having a comorbid condition—most often an anxiety disorder (59%), substance use disorder (24%), or impulse control disorder (30%). More recently, a third-wave NCS data collection was confined to adolescents (N = 10,123) aged 13 to 18. These investigators reported a lifetime prevalence rate of 14% for a mood disorder (which actually included borderline personality disorder) (Merikangas et al., 2010) and a previous 12-month prevalence of 8% (Kessler et al., 2012). Again, "about 40% of affected youth. . . reported more than one class of lifetime disorder, with mood disorder being the most likely to co-occur with other classes" (Merikangas et al., 2010, p. 987).

Comorbidity, however, can in some cases suggest a problem for the diagnostic manual; more specifically, the lack of distinct boundaries between two independent diagnoses and perhaps even the presence of a common shared pathology (Widiger & Gore, 2012). For example, Krueger and Markon (2006) have written extensively about the meanings of "comorbidity;" they discuss whether or not effective treatments target situational mental disorders or more core, long-term processes (Krueger & Markon,

2006). As expressed by the vice chair of DSM-5, "the failure of DSM-III criteria to specifically define individuals with only one disorder served as an alert that the strict neo-Kraepelinian categorical approach to mental disorder diagnoses advocated by Robins and Guze (1970), Spitzer, Endicott, & Robins (1978), and others could have some serious problems" (Regier, 2008, p. xxi). In an effort to address one form of comorbidity involving anxiety and depression, a diagnosis of mixed-anxiety depressive disorder was proposed for DSM-5 (as well as for DSM-IV) that explicitly acknowledged the large numbers of persons who could not be distinguished as having either an anxiety or a mood disorder (Katon & Roy-Byrne, 1991; Presig, Merikangas, & Angst, 2001), albeit this disorder would have been arbitrarily classified as a mood disorder in DSM-5 (this proposal, however, has been withdrawn).

Most (if not all) mental disorders appear to be the result of a complex interaction of an array of biological vulnerabilities and dispositions with a number of significant environmental/psychosocial events that often exert their progressive effects over a developing period of time (Rutter, 2003). There may never be a single gene that is *the* cause of a particular mental disorder. Each individual's mental disorder is more likely to be the result of an array of genetic dispositions and vulnerabilities (Frances & Widiger, 2012). The symptoms and pathologies of mental disorders are also highly responsive to a wide variety of neurobiologic, interpersonal, cognitive, and other mediating and moderating variables that help to develop, shape, and form a particular individual's psychopathology profile. This complex etiological history and individual psychopathology profile are unlikely to be well described by single diagnostic categories that attempt to make distinctions at nonexistent discrete joints along the continuous distributions (Widiger & Samuel, 2005). As expressed by Kupfer, First, and Regier (two of whom are the chair and vice chair of DSM-5):

> Epidemiologic and clinical studies have shown extremely high rates of comorbidities among the disorders, undermining the hypothesis that the syndromes represent distinct etiologies. Furthermore, epidemiologic studies have shown a high degree of short-term diagnostic instability for many disorders. With regard to treatment, lack of treatment specificity is the rule rather than the exception. (Kupfer, First, & Regier, 2002, p. xvii)

The categorical model of classification is failing in many ways, including an absence of a provision of reliably distinct boundaries, an absence of a credible rationale for diagnostic thresholds, an inadequate coverage of existing clinical populations, and the absence of specific etiologies and treatments (Kupfer et al., 2002; Widiger & Samuel, 2005). Nowhere is this more evident than in the classification of mood disorders. For example, depression is a section of the diagnostic manual that does have considerable difficulty identifying or defining a clear boundary with "normal" sadness. Narrow, Rae, Robins, and Regier (2002) proposed raising the threshold for a mood disorder diagnosis in response to the perception that the prevalence rates reported in the NCS and other comparable studies were felt to be excessively high and certainly much larger than could be currently treated. However, even subthreshold cases of depression (i.e., persons with depressive symptoms below the existing threshold for a DSM-IV-TR mental disorder diagnosis) are responsive to pharmacologic interventions, seek treatment for their sadness, and are often being treated within primary care settings (Judd, Schettler, & Akiskal, 2002; Magruder & Calderone, 2000; Pincus, McQueen, & Elinson, 2003). Kessler, Merikangas et al. (2003) reported that "elevated risk of [negative life] outcomes among mild cases versus noncases is consistently larger than the elevated risk among moderate cases versus mild cases" (p. 1121). Kessler, Merikangas et al. argued that "mild cases should be retained in the definition of disorders" (p. 1121) to acknowledge that "mental disorders (like physical disorders) vary in severity" (p. 1121). In fact, because persons with subthreshold levels of depression are seeking and are responsive to treatment, there was a proposal to include within an appendix to DSM-IV (but not considered for DSM-5) a diagnosis of "minor depressive disorder," which it is acknowledged "can be difficult to distinguish from periods of sadness that are an inherent part of everyday life" (American Psychiatric Association, 2000, p. 776).

A common view is that most instances of sadness do not constitute a mental disorder and that a major depressive disorder is qualitatively distinct from normal sadness (Horwitz & Wakefield, 2007; Wakefield, 2001). However, a simple inspection of the diagnostic criteria for major depressive disorder would not lend confidence to a conceptualization of this condition as being something uniquely different from "normal" depression or sadness (Andrews et al., 2008). Persons who are just very sad may have most of the same attributes as those with a major depressive disorder (if not all of them) but just at a lesser degree of severity (Lamb et al., 2010). The

diagnostic criteria for major depressive disorder include depressed mood, loss of interest or pleasure, weight loss (or gain), insomnia (or hypersomnia), psychomotor retardation (or agitation), loss of energy, feelings of worthlessness, and/or diminished capacity to make decisions (American Psychiatric Association, 2000). Each of these diagnostic criteria is readily placed along a continuum of severity that would shade imperceptibly into what would be considered a "normal" sadness or depression. DSM-IV-TR, therefore, includes specific thresholds for each of them, but these required thresholds are clearly arbitrary points of demarcation that simply distinguish a relatively higher level of severity from a lower level of severity (e.g., "nearly every day" or "markedly diminished," and at least a "two week" period; American Psychiatric Association, 2000, p. 356). The diagnosis requires five of these nine criteria, with no apparent rationale for this threshold other than it would appear to be severe enough to be defensible to be titled as a "major" depressive episode as distinguished from a "minor" depressive episode, which is then distinguished from "normal" sadness (American Psychiatric Association, 2000).

There is little empirical support for the belief that there is a qualitative distinction between normal sadness and clinical depression (Andrews et al., 2008; Goldberg, 1996). Kessler, Zhao, Blazer, and Swartz (1997) examined the distribution of minor and major symptoms of depression using data from the first NCS study. They considered the relationship of these symptoms with parental history of mental disorder, number and duration of depressive episodes, and comorbidity with other forms of psychopathology. Respective relationships increased with increasing number of symptoms, with no clear distinct break. This finding was replicated in the second NCS study when Kessler, Merikangas et al. (2003) compared four levels of severity of depression (as well as other disorders) with respect to a 10-year follow-up of 5,463 cases with respect to hospitalization, work disability, and suicide attempts. "No consistent inflection point in the gradient of outcome risk [could] be found" (p. 1121). Ustun and Sartorius (1995) conducted a study of 5,000 primary care patients in 14 countries and reported a simple linear relationship between disability and number of depressive symptoms. Sakashita, Slade, and Andrews (2007) examined the relationship between the number of symptoms of depression and four measures of impairment using data from the Australian National Survey of Mental Health and Well-Being and found that the relationship was again linear, with no clear or natural discontinuity to support the selection of any particular cutoff point to distinguish between normal and clinical depression.

Taxometric analyses is a series of related statistical techniques to detect whether a set of items is optimally understood as describing (assessing) a dimensional or a categorical construct, providing thereby a direct test of which structural model is most valid in characterizing the set of items or variables (Ruscio, & Ruscio, 2004). A number of taxometric studies have been conducted on measures of depression. The first was provided by Ruscio and Ruscio (2000), analyzing items from the Beck Depression Inventory and, independently, items from the Zung Self-Rating Depression Scale in a sample of 996 male veterans who had received a diagnosis of posttraumatic stress disorder but also had a high prevalence rate of major depressive disorder; they also studied a sample of 8,045 individuals from the general population (60% female) who completed the items from the Depression scale of the Minnesota Multiphasic Personality Inventory. The investigators indicated that "results of both studies, drawing on three widely used measures of depression, corroborated the dimensionality of depression" (Ruscio & Ruscio, 2000, p. 473). The taxometric findings of Ruscio and Ruscio (2000) have subsequently been replicated many times over (e.g., Prisciandaro & Roberts, 2005), with only a few scattered failures (Widiger & Edmundson, 2011).

As expressed by the chair and vice-chair of DSM-5, "we have decided that one, if not the major, difference between DSM-IV and DSM-V will be the more prominent use of dimensional measures in DSM-V" (Regier, Narrow, Kuhl, & Kupfer, 2009, p. 649; [the original acronym for DSM-5 was DSM-V]). In 1999, the DSM-5 Research Planning Conference was held under joint sponsorship of the American Psychiatric Association and the National Institute of Mental Health (NIMH), the purpose of which was to set research priorities that would optimally inform future classifications. An impetus for this effort was frustration with the existing nomenclature (Kupfer et al., 2002). At this conference, research planning work groups were formed to develop white papers that would set a research agenda for DSM-5. The Nomenclature Work Group, charged with addressing fundamental assumptions of the diagnostic system, concluded that it is "important that consideration be given to advantages and disadvantages of basing part or all of DSM-V on dimensions rather than categories" (Rounsaville et al., 2002, p. 12).

The white papers developed by the research planning work groups were followed by a series of international conferences whose purpose was to further enrich the empirical data base in preparation for the eventual development of DSM-5. The final conference was devoted to developing dimensional approaches for classification across the entire diagnostic manual (Helzer, Kraemer et al., 2008), including major depressive disorder (Andrews et al., 2008). It is evident that a primary goal for DSM-5 is to shift the manual toward a dimensional classification (Helzer, Wittchen, Krueger, & Kraemer, 2008). "The single most important precondition for moving forward to improve the clinical and scientific utility of DSM-V will be the incorporation of simple dimensional measures for assessing syndromes within broad diagnostic categories and supraordinate dimensions that cross current diagnostic boundaries" (Regier et al., 2009, p. 649).

Nevertheless, the shifts to be taken in DSM-5 are unlikely to be fundamental or perhaps even significant. "What is being proposed for DSM-V is not to substitute dimensional scales for categorical diagnoses, but to add a dimensional option to the usual categorical diagnoses for DSM-V" (Kraemer, 2008, p. 9). As acknowledged by Helzer, Kraemer, and Krueger (2006), "our proposal not only preserves categorical definitions but also does not alter the process by which these definitions would be developed. Those charged with developing criteria for specific mental disorders would operate just as their predecessors have" (p. 1675). Dimensional proposals for DSM-5 are made only to develop "supplementary dimensional approaches to the categorical definitions that would also relate back to the categorical definitions" (Helzer, Wittchen, et al., 2008, p. 116). These dimensions will serve only as ancillary descriptions that will lack any official representation within a patient's medical record (i.e., they will have no official alphanumerical code and may then not even be communicated to any public health-care agency). For major depression, for instance, the proposal is limited to the inclusion of an optional supplementary rating of severity of depression. In sum, "what is being proposed for DSM-V is not to substitute dimensional scales for categorical diagnoses, but to add a dimensional option to the usual categorical diagnoses for DSM-V" (Kraemer, 2008, p. 9). In the end, DSM-5 will remain a categorical diagnostic system.

Shifting to a Neurobiological Model

The first editions of the DSM favored the psychodynamic theoretical model. The authors of DSM-III removed terms (e.g., *neurosis*) that appeared to refer to psychodynamic constructs in order to have the manual be atheoretical or at least be reasonably neutral with respect to alternative models of psychopathology (Spitzer et al., 1980). This approach, however, has not been well received by proponents of these alternative theoretical perspectives. Interpersonal and systems theorists, who consider dysfunctional behavior to be due to a pathology of a wider social system rather than simply within the individual, consider the organismic diagnoses of DSM-IV-TR to be fundamentally antithetical to their theoretical perspective (Reiss & Emde, 2003). Psychodynamically oriented clinicians bemoan the fact that as the succeeding editions of the manual have become increasingly objective, descriptive, and atheoretical, they have inevitably minimized the inferential, dynamic aspects of diagnosis on which most psychodynamically oriented clinicians depend. They have now constructed their own diagnostic manual, the *Psychodynamic Diagnostic Manual* (PDM Task Force, 2006). Behaviorists argue that the organismic perspective of DSM-IV-TR is inconsistent with the situational context of dysfunctional behavior (Folette & Houts, 1996). Even neurobiologically oriented psychiatry is dissatisfied. "Although there is a large body of research that indicates that a neurobiological basis for most mental disorders, the DSM definitions are virtually devoid of biology" (Charney et al., 2002, pp. 31–32). Of course the dissatisfaction of each theoretical perspective with the DSM-IV-TR might be consistent with the effort to avoid any theoretical bias or favoritism.

The aspiration to be atheoretical, though, is slowly but surely dissipating. Whereas DSM-I favored a psychodynamic perspective (American Psychiatric Association, 1952; Spitzer et al., 1980), the American Psychiatric Association and NIMH are shifting explicitly toward a neurobiologic orientation. This is evident in a number of ways, both implicitly and explicitly. For example, a reading of the table of contents of any issue of the two leading journals of psychiatry (i.e., *American Journal of Psychiatry* and *Archives of General Psychiatry*) will evidence a strong neurobiologic orientation for most of the articles. DSM-IV included a new section of the text devoted to laboratory and physical exam findings (Frances et al., 1995). All of the laboratory tests included therein were concerned with neurobiologic findings, with no reference to any laboratory test that would be of particular relevance to a cognitive, psychodynamic, or interpersonal-systems

clinician (this section is likely to be modified and/or extended in DSM-5 to include genetic and physiologic risk factors; Kupfer & Reiger, 2011). The definition of mental disorder in DSM-5 will likely refer to an underlying "psychobiological dysfunction" in recognition that "all behavior and psychology are dependent upon brain processes" (Stein et al., 2010, p. 5). The head of NIMH has indicated that priority for funding in the future will be given to studies that formally adopt a "clinical neuroscience" perspective that contributes to an understanding of mental disorders as "developmental brain disorders" (Insel, 2009, p. 132). This is being accomplished in part through the NIMH development of research domain criteria (RDoC; Insel et al., 2010) "with a strong focus on biological processes, and emphasis on neural circuits" (Sanislow et al., 2010, p. 633). "The RDoC framework conceptualizes mental illnesses as brain disorders" (Garvey et al., 2010, p. 749). As indicated by Miller (2010), "over the next 2 to 3 years, NIMH will encourage researchers to shift from using DSM criteria in their grant proposals to using the RDoC categories" (p. 1437), such as "fear circuitry disorder." In an editorial concerning "neuroscience, clinical evidence, and the future of psychiatric classification in DSM-5," Kupfer and Regier (2011, p. 1), the chair and vice-chair of DSM-5, embraced this shifting tide, stating that "this NIMH objective is consistent with our research planning conferences and conclusions" (p. 2).

It is unlikely that one could create a diagnostic manual that is entirely neutral or atheoretical. However, a professional nomenclature should probably at least aspire to remain neutral with respect to alternative theoretical models, particularly in the absence of any obvious superiority of one theoretical perspective relative to another with respect to etiology, pathology, and treatment (Widiger, 2013). Mental disorders cannot currently be diagnosed solely on the basis of neurobiological mechanisms or fully understood solely with respect to them (Kendler, 2005). The DSM is used by clinicians and researchers from a wide variety of theoretical perspectives, including (but not limited to) neurobiological, psychodynamic, interpersonal, cognitive, behavioral, humanistic, and interpersonal-systems theoretical perspectives. An important function of the manual is to provide a common means for communication among and research concerning these competing theoretical orientations in a language that would not favor one perspective over the other (Frances et al., 1989). A language that purposely favors one particular perspective would not provide an equal playing field and would bias subsequent scientific research and discourse (Wakefield, 1998). It might be impossible to construct a diagnostic manual that is truly theoretically neutral, but this is not a compelling reason for abandoning the effort, particularly if the manual is to be used for research attempting to determine the validity of alternative theoretical perspectives.

Conclusions

Nobody is fully satisfied with DSM-IV-TR or lacks valid criticisms of it. This is unlikely to change with DSM-5. DSM-IV-TR is a well-reasoned document developed by leading experts based on their review of a considerable body of existing research, but there is no way to prove conclusively the presence and/or validity of any particular mental disorder diagnosis (Meehl, 2010; Strauss & Smith, 2009). There will always be at least some degree of controversy. In addition, as an official diagnostic nomenclature, the DSM is an exceedingly powerful and influential social document, impacting a wide range of social issues and personal lives. Nobody, however, appears to suggest that all official diagnostic nomenclatures should be abandoned. The benefits do appear to outweigh the costs (Salmon et al., 1917; Stengel, 1959). Everybody finds fault with this language, but it is clearly important and perhaps necessary for consistent clinical and research communication to have an official diagnostic nomenclature.

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CHAPTER

3

From Comorbidity to Constructs: Recurring and Emergent Issues in Modeling Comorbidity

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Abstract

Comorbidity models have become central to psychopathology theory and research, not only because they have clarified our understanding of how and why disorders co-occur but also because they have clarified our understanding of what the disorders are. This chapter reviews basic types of comorbidity models, recurring issues in comorbidity modeling, and discuss emerging issues in the area. Using recent epidemiological, repeated-measures data on depression and anxiety as an example, two different models of comorbidity are compared, one in which comorbidity arises due a shared liability dimension (i.e., a reflective or latent variable model) and another in which comorbidity arises as an epiphenomenon of correlated symptoms (i.e., a formative or network model). This comparison, relatively novel in the literature, illustrates a number of issues that are encountered in comorbidity modeling, and clearly demonstrates how questions pertaining to comorbidity can shape our understanding of psychopathology constructs.

Key Words: reflective and formative measurement, midlife, development, daily interview

Introduction

Like many extensively studied constructs, comorbidity has a multitude of meanings and interpretations and is associated with certain recurring theoretical and methodological issues. This is perhaps especially true when discussing comorbidity in the context of depression, which is one of the most common and costly forms of illness worldwide (Moussavi et al., 2007). Given its associations with so many medical, sociological, and psychological variables, different forms and aspects of depressive comorbidity will have differential emphasis and salience in different contexts.

The purpose of this chapter is to review the various meanings and interpretations of comorbidity in empirical modeling and research, so as to frame discussion, prevent confusion, and contribute to progress in understanding depression and its comorbidity with various conditions. Newly emergent themes in the study of comorbidity will also be discussed. This chapter hopefully will illustrate that comorbidity has fundamental implications for understanding not only the causes and consequences of depression but also the nature of depression itself.

Comorbidity Paradigms: Co-occurrence Versus Covariance

The study of comorbidity has an extensive history, as it applies to depression specifically as well as it applies to psychopathology and illness more generally. Comorbid phenomena have undoubtedly been studied for some time, although the term was in established use by the middle of the twentieth century (although Feinstein [1970] is often credited for the term, "comorbidity" was in established use prior to that time, appearing in texts in the 1960s [e.g., Gale Research Group, 1965]). Discussion and study of psychiatric comorbidity began to accelerate

in the 1980s and 1990s, following publication of the third edition of the *Diagnostic and Statistical Manual* (DSM-III), and currently remains a topic of widespread attention.

Relatively early in the emerging literature on comorbidity, it became clear that two paradigms for understanding comorbidity predominate (Lilienfeld, Waldman, & Israel, 1994). The first, referred to here as the *exogenous co-occurrence* paradigm, focuses on the co-occcurrence of two or more conditions in individuals and the effects of this co-occurrence on other variables. The second paradigm, referred to here as the *endogenous covariance* paradigm, focuses on associations between two or more conditions in a group of individuals, and explaining the causes of this covariance. The terms "exogenous" and "endogenous" are used here as they are used in the structural equation modeling literature (Bollen, 1989), where they refer to scenarios where causes are, respectively, outside of the model (and are therefore ignored) or are inside of the model (and are therefore included). Although many cases of research and theory blur the distinction between these two paradigms, they nevertheless represent major approaches to understanding comorbidity.

Comorbidity as Co-occurrence

The first paradigm is arguably the older of the two and represents the original focus of comorbidity theory and research. The earliest discussions of comorbidity emphasized effects of co-occurring conditions on outcome, a perspective that continues into current theory and research. Feinstein (1970), for example, defined comorbidity as the presence of "any distinct additional clinical entity that has existed or that may occur during the clinical course of a patient who has the index disease under study," emphasizing discussion of its "functional" and "intellectual effects on clinical outcome."

Figure 3.1a illustrates the exogenous co-occurrence paradigm. In this paradigm, two disorders, A and B, affect some outcome. Each of the disorders may influence the outcome directly, but their joint presence in an individual may also have special significance, such that they interact with one another in influencing the outcome. A prototypic exogenous co-occurrence model is essentially a moderation or interaction model, where an additional disorder moderates the effects of another variable, typically by amplifying some effect. The disorders are also assumed to be independent of one another, or approximately so, and are treated as exogenous variables (variables whose causes are assumed to be outside the scope of the model). A hypothetical example might involve psychosis, cancer, and their impact on social functioning: the two former variables are etiologically distinct, with causes outside the scope of the model. They may interact, such that the combination of the two in a single individual might have effects beyond their sum.

Comorbidity as Covariance

Central to the exogenous co-occurrence paradigm is the assumption that the comorbid disorders are distinct and that their causes can be treated as outside the scope of the model. Although this assumption is often appropriate for comorbidity between certain psychiatric and nonpsychiatric disorders (e.g., psychosis and cancer), its

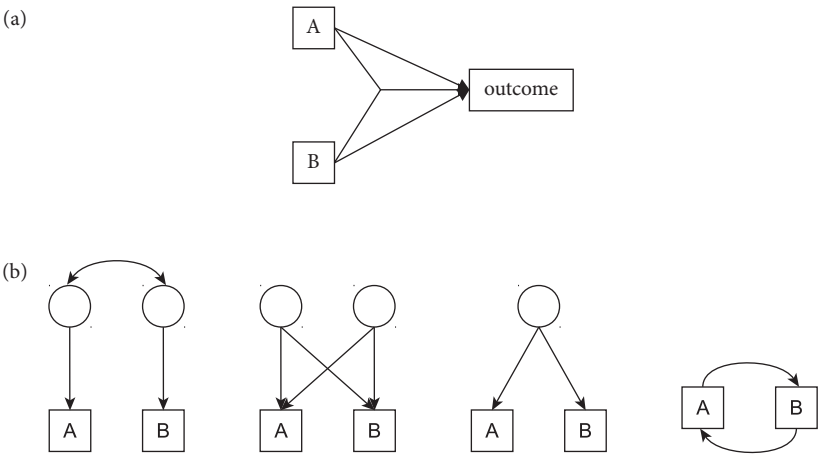

Figure 3.1 Illustrations of exogenous co-occurrence (A) and endogenous covariance (B) models. In both figures, the rectangles indicate disorders or outcomes of interest; circles represent liabilities underlying the disorders.

appropriateness for many other forms of comorbidity is unclear. In many settings, the causes of the two disorders are central to the theoretical model (i.e., are endogenous to the model), such as when the two disorders share etiology or influence one another. In such cases, comorbidity is generally more fruitfully conceived of in terms of covariance between disorders, the etiology of which is to be explained.

As many authors have noted (Lilienfeld et al., 1994), the etiology of psychopathology is usually unclear, to the extent that it is often unclear how to delineate distinct disorders. In such cases, comorbidity may reflect different manifestations of the same underlying pathology or state rather than co-occurrence of or associations between distinct processes. Even in cases where the distinction between disorders is relatively clear or well-established, one may influence another—or they may mutually influence one another—in a way that makes the assumption of exogenous causes inappropriate. For example, depression and diabetes are clearly distinct disorders, but it is reasonable to expect that diabetes might affect levels of depression, or conversely, that depression might affect severity of diabetes (e.g., through lack of self-care).

Figure 3.1b illustrates commonly encountered features of endogenous covariance models. Note that in actual application, various features of these models might be combined in a single account, and that the models as illustrated are not necessarily identified as they are presented. Also, although only two disorders are included in the figures, in practice models often incorporate multiple disorders simultaneously (i.e., "multimorbidity"; van den Akker, Buntinx, & Knottnerus, 1996).

As is illustrated in the figures, comorbidity between disorders may be induced by multiple distinct causes being correlated with one another. It may also be induced by through multiple, distinct causes having multiple effects. This latter model can be distinguished from the former with enough measurements in that it requires more parameters to capture patterns of comorbidity in the data. This can be seen in the relative number of paths of the two models in Figure 3.1b. The second, multiple-effects model predicts more differentiated patterns of covariance between specific pairs of disorders, because each disorder has a unique path from each liability. As illustrated in the third diagram of Figure 3.1b, comorbidity may also be induced through multiple disorders acting as different manifestations of the same underlying process. This can be thought of as an even more constrained version of the first model, where the correlation between disorders is perfect. Finally, comorbidity may be induced through direct influences of conditions on one another. Comparisons of these sorts of direct-effects models against the other models often require complex designs, such as behavior genetic or longitudinal designs. They can generally be distinguished from the other models in that they imply that specific correlations involving a pair of disorders cannot easily be predicted from other correlations being modeled (e.g., that the within-twin correlation between two disorders is relatively distinct from the cross-twin correlation between those two disorders).

Syndrome Models of Comorbidity

Over the past decade, numerous researchers have begun to investigate and compare these different explanations for comorbidity between syndromes. These investigations have revealed that many syndromes traditionally assumed to be distinct may actually reflect the same underlying pathologies. More broadly, these studies have raised important questions about what is shared between syndromes, what is unique about a particular syndrome, and how to conceptualize these issues.

Liability Dimensions

A number of studies, for example, have modeled comorbidity between multiple disorders in terms of underlying liability dimensions, presumed to reflect pathological processes underling the disorders. In general, these studies have outlined three broad, replicated liability dimensions that might account for patterns of comorbidity (e.g., Kotov et al., 2011; Wolf et al., 1988). The first of these, generally referred to as internalizing, is reflected in disorders characterized primarily by negative emotion, such as depression, phobias, and posttraumatic stress syndromes. The second, generally referred to as externalizing, is reflected in disorders such as conduct disorder and other antisocial behavior disorders, as well as substance use disorders. The third liability dimension reflects thought disorder, including schizophrenia and the psychotic disorders.

Although these studies initially focused on cross-sectional analyses of disorders in clinical and epidemiological samples, they have expanded to include more etiologically informative designs, such as longitudinal and family studies. The results of these studies have largely supported the conclusions of the cross-sectional designs and also clarified the important role of the superordinate liability factors

in prediction. For example, patterns of genetic and environmental relationships largely parallel phenotypic relationships along the lines of the superordinate liability dimensions. Internalizing disorders are likely to segregate together among twins, as are the externalizing disorders (Kendler, Prescott, Myers, & Neale, 2003). In longitudinal studies, similarly, the superordinate liability dimensions account for a large proportion of the variance in predicting stability of disorder, as well as outcomes (Fergusson, Horwo-od, & Boden, 2006; Seeley, Kosty, Farmer, & Lewinsohn, 2011).

For example, research by Fergusson et al. (2006) indicates that a majority of the stability in depression over time can be accounted for by general internalizing liability rather than disorder-specific effects. Specifically, depression tends to predict other internalizing disorders at other times at levels comparable to depression at other times. In other words, the cross-time, cross-disorder correlation is similar in magnitude to the cross-time, within-disorder correlation. Seeley et al. (2011) similarly found that superordinate internalizing liability accounted for a majority of the variance in psychosocial functioning and family psychiatric history; specific disorders contributed little in predicting functioning or family psychiatric status.

Parsing Shared and Unique Components of Disorders

Although superordinate liabilities such as internalizing and externalizing account for much of the comorbidity between disorders, they do not account for all of it. Subsets of disorders share variance beyond the broad superordinate factors. Among the internalizing disorders, for example, the phobias and panic disorder appear to share common variance beyond general internalizing liability, suggesting the presence of a specific fear liability in addition to general internalizing. Depression and generalized anxiety also share variance beyond general internalizing, suggesting the presence of a distress liability (Krueger & Markon, 2006).

These general patterns highlight a hierarchy of shared and unique etiologies accounting for comorbidity between disorders. Some of these etiologies are shared by a large spectrum of disorders (e.g., the internalizing disorders), some of these etiologies are shared by a smaller subset of disorders (e.g., the fear disorders), and some etiologies are disorder-specific. In this regard, it is important to recognize that any theory explaining comorbidity must take into account the scope of disorders being examined. A study of the comorbidity between depression and generalized anxiety, for example, might miss

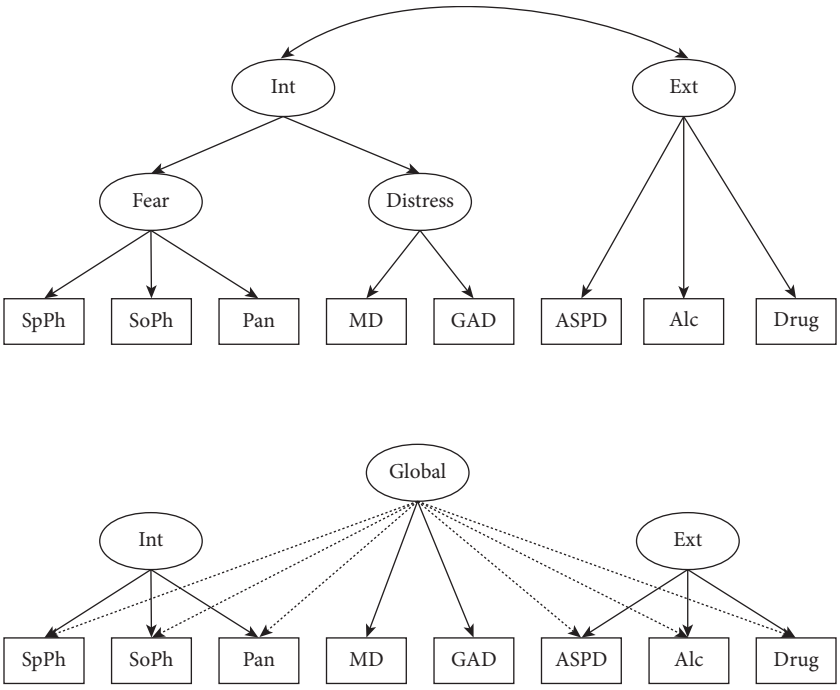

Figure 3.2 Illustration of two different liability models of common forms of psychopathology.

Int, internalizing; Ext, externalizing; SpPh, specific phobia; SoPh, social phobia; MD, depression; xGAD, generalized anxiety disorder; ASPD, antisocial personality disorder; Alc, alcohol use disorder; Drug, other drug disorder.

the contribution of general internalizing liability if other internalizing disorders, such as panic and phobia, were not also included.

The hierarchical nature of liabilities underlying comorbidity has sometimes led to differing perspectives on how to interpret the nature of those liabilities, in terms of how general and specific components of liability are distributed among disorders or influence those disorders. An example of this is illustrated in Figure 3.2, which represents two different accounts of the nature of factors underlying comorbidity patterns (Krueger & Markon, 2006; Lahey, Van Hulle, Singh, Waldman, & Rathouz, 2011). Both accounts comprise three superordinate liabilities: an externalizing liability, a liability primarily affecting depression and generalized anxiety, and a liability affecting the phobias and panic. In the top account, however, two of the liabilities, distress and fear, both reflect a common internalizing dimension (Krueger & Markon, 2006); in the bottom account, there is one internalizing liability, and another global liability that affects all disorders, but depression and generalized anxiety most strongly (Lahey et al., 2011).

The relationship between the distress disorders (depression and generalized anxiety) and the other mental disorders is key to distinguishing the two accounts. The top account predicts that the distress disorders will be more strongly related to the other internalizing disorders than to the externalizing disorders; the bottom account predicts that the distress disorders will be equally related to the other internalizing disorders and externalizing disorders. Thus far, available evidence across studies seems to support the top model, as the distress disorders generally seem to be more strongly related to the fear disorders than to the externalizing disorders (Beesdo-Baum et al., 2009; Kessler et al., 2011; Krueger & Markon, 2006). However, relatively few studies have formally evaluated the bottom model.

Overall, work on syndrome comorbidity suggests that syndromes can be understood in terms of underlying liability factors. Disorders characterized by negative emotion—the depression, anxiety, and fear disorders—can be understood in terms of a common internalizing factor, for example. Disorders such as antisocial personality disorder, conduct disorder, and the substance use disorders can be understood in terms of a common externalizing factor. A similar psychosis liability factor can also be identified (e.g., Kotov et al., 2011; Wolf et al., 1988). These liability factors are organized hierarchically, moreover, so that in addition to broad liability factors influencing many disorders, more specific factors influence subsets of disorders. For example, in addition to being influenced by broad internalizing liability, the phobias and panic disorder are likely influenced by a more specific fear liability, characterized by acute, paroxysmal fear responses. Further research is needed to clarify the nature of this hierarchy, to understand how liabilities can be most accurately parsed into broader and more specific components.

Symptom Models of Comorbidity

As models of comorbidity between disorders have become more complex, and it has become clear that there are hierarchies of shared relationships, attention has increasingly been focused on the symptoms underlying those disorders in providing explanations for comorbidity. For example, understanding patterns of relationships among specific internalizing symptoms would help clarify what is distinctive about the distress versus fear disorders and what is shared between them.

One fundamental concern underlying this interest in symptom-level explanation of comorbidity is heterogeneity of criteria within a single diagnosis. Although some diagnoses are relatively homogeneous in their symptom criteria, other diagnoses are more heterogeneous. If disparate pathologies are reflected in a single diagnosis, it becomes challenging to understand which pathologies account for comorbidity with another diagnosis—all of the pathologies causing the disorder, or a subset of them? Do those pathological processes relate in different ways to those in another diagnosis? More broadly, do spurious features of the diagnostic criteria account for comorbidity patterns? For example, do disorders with the same impairment or duration criteria—which are relatively arbitrary—covary more than other disorders, simply because of those criteria, independently of more core pathological processes?

Posttraumatic stress disorder (PTSD) illustrates well complexities that arise in explaining comorbidity in the presence of relatively heterogeneous symptom criteria. In recent years, various studies have demonstrated that PTSD can be understood in terms of four subordinate dimensions: one reflecting dysphoria, another reflecting intrusive cognitions, another reflecting avoidant behavior, and another reflecting hypervigilance (Yufik & Simms, 2010). Importantly, these four dimensions relate differentially to other disorders in theoretically meaningful ways. In this account, in order to completely

characterize comorbidity with PTSD, it is necessary to examine PTSD at the level of symptoms, rather than disorder. For example, the relationship between PTSD and depression appears to be largely mediated through the dysphoria symptoms of PTSD, with no contribution from the hypervigilance symptoms (Gootzeit & Markon, 2011). The relationship between panic and PTSD, in contrast, appears to be mediated both through dysphoria as well as hypervigilance (Gootzeit & Markon, 2011).

In this case, focusing on the comorbidity between depression and PTSD at the level of syndromes would obscure more meaningful relationships that are mediated through liability factors manifested at the level of symptoms. This is especially important because the symptom liability factors exhibit differential patterns of relationships with other disorders, differentiable in magnitude as well as quality. For example, the relationship between depression and dysphoria is not only stronger than the relationship between depression and hypervigilance, but it is strong enough to suggest that depression and the dysphoria of PTSD are identical (Gootzeit & Markon, 2011). This has important implications for understanding the nature of PTSD, in terms of understanding what components of PTSD are unique relative to other internalizing disorders (Yufik & Simms, 2010). It also has important implications for clinical assessment, in that it suggests some criteria of PTSD are redundant with and might be better characterized by other forms of internalizing psychopathology (Breslau, Chase, & Anthony, 2002; Yufik & Simms, 2010).

Liability Symptom Models

Various researchers have examined the liability factors suggested by models such as those presented in Figure 3.2, as they affect symptoms rather than disorders. For example, I recently analyzed data from the 2000 British Psychiatric Morbidity surveys, a large-scale epidemiological survey of mental disorder in Britain, to determine how general liability factors manifest in symptoms across a broad range of disorders (Markon, 2010). These analyses identified 20 subordinate syndromes, similar but not identical to disorders defined in official nosologies, that could be described in terms of 4 superordinate liability factors. In addition to internalizing, externalizing, and thought disorder, which have been identified in diagnostic-level studies, this analysis also identified a pathological introversion factor, reflected in problems related to social anxiety, lack of assertiveness, and dependency.

Various researchers have also examined symptoms within each of the superordinate spectra (for example, only internalizing symptoms, or only externalizing symptoms). Watson and colleagues (2007), for example, have examined the structure of internalizing psychopathology at the level of symptoms, delineating a number of subordinate factors that are broadly influenced by a single internalizing dimension. Krueger and colleagues, similarly, have examined the structure of externalizing symptoms (2007), identifying, in addition to a general externalizing factor, superordinate aggression and substance use factors as well. Similar analyses have been conducted on the structure of psychotic symptoms (Dikeos et al., 2006), identifying positive symptom (e.g., hallucinations and delusions), negative symptom (e.g., alogia and blunted affect), and disorganization factors.

Interestingly, in the work of both Watson et al. (2007) and Markon (2010), distinct superordinate fear and distress factors were not identified (although subordinate depression, anxiety, and phobia factors were). These results suggest that the superordinate distress and fear factors suggested in Figure 3.2 may reflect an artifact of official diagnostic conventions or assessment procedures (however, see also Beesdo-Baum et al., 2009, and Kessler et al., 2011, who find similar results). This result also supports the model in the top of Figure 3.2, insofar as it suggests that at the level of symptoms, depression is not easily separated from phobias, and that forms of internalizing psychopathology, including depression, are more closely related to one another than to externalizing. Future studies are needed to replicate these findings, however.

Formative Symptom Models

In the models just described, comorbidity between disorders, either at the level of symptoms or diagnoses, is explained in terms of underlying liability factors. It is possible, however, to conceive of comorbidity in terms of direct relationships between the symptoms, that induce comorbidity in the diagnoses as a sort of epiphenomenon related to the way disorders are defined. These sorts of models have been referred to recently as network models (Cramer, Waldorp, van der Maas, & Borsboom, 2010), although similar ideas have been discussed in the past (e.g., Caron & Rutter, 1991; Lilienfeld, Waldman, & Israel, 1994; Pfeffer & Plutchik, 1989). They are referred to here as formative models to maintain consistency with the psychometric literature, where formative measurement models

have been explored in great detail as an alternative to liability models (Blalock, 1964; Edwards & Bagozzi, 2000; Fornell & Bookstein, 1982; Howell, Breivik, & Wilcox, 2007a, 2007b). Liability models are generally referred to as reflective models in that literature, as the indicators reflect underlying liability; formative models are referred to as such because the indicators form or cause the constructs.

Figure 3.3 illustrates a hypothetical formative model. The symptoms of Disorders A and B are all correlated with one another. Although the symptoms are shown as having nondirectional relationships in the figure (i.e., with double-headed arrows), the relationships could be directional (e.g., lack of sleep causing concentration problems). The symptoms define the disorders, and in this sense "cause" the disorders. The direction of association between the symptoms and disorders goes from the former to the latter—unlike in Figure 3.2, where the direction goes from liability factors to the symptoms. For example, hypersomnia and guilt would not be related because they are caused by depression, but because, for instance, hypersomnia might lead to guilt, and the two symptoms "happen" to define depression. In fact, in an important sense, under a formative model, depression does not exist at all as a real entity—only its symptoms exist, with depression being an externally imposed construct.

Certain features of the formative model are important to emphasize. First, in a strict formative model, the symptoms are assumed to be measured without error—there are no influences on the symptoms that are not directly observed. Most importantly, there are no disorders causing the symptoms, and in a strict sense, there are no symptoms at all—there are perfectly measured criteria that are used to define disorders. Second, relatedly, the disorders do not exist outside of the symptoms—in some sense, they are summaries of certain sets of symptoms. In fact, strictly speaking, there cannot be other symptoms of a given disorder; a disorder defined by other criteria would technically be a different disorder.

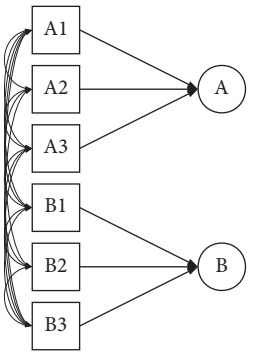

Figure 3.3 Illustration of a strict formative model.

Rectangles indicate criteria, circles indicate disorders. Note that the disorders are entirely defined by the criteria; the directed paths (with single-headed arrows) in many circumstances would be fixed and not estimated.

Under a strict formative model, two disorders (for example, A and B in Figure 3.3) will exhibit comorbidity only because their symptoms are directly associated with one another. Comorbidity is then an epiphenomenon, a side effect of the fact that correlated symptoms are used to define disorders. In this regard, formative models differ in important but potentially subtle ways from the models illustrated in Figure 3.1b. Unlike the first three models illustrated in Figure 3.1b, comorbidity is not caused by shared liabilities, but rather because directly correlated symptoms are used to define the two disorders. Unlike the last model in Figure 3.1b, the disorders do not have causal effect themselves (for example, depression per se cannot cause something) and are therefore not able to influence one another—the direct relationships instead are at the level of the symptoms defining the disorders. Under a strict formative model, depressive disorder and generalized anxiety disorder are not comorbid because they share common causes, or because they influence one another, but because some of their symptoms cause one another.

Very little research has been conducted to evaluate formative models as explanations of comorbidity. Also, as some have noted, it is unclear how different formative models actually are from existing liability models (Danks, Fancsali, Glymour, & Scheines, 2010; Humphry & McGrane, 2010; Molenaar, 2010). For instance, it is possible to model direct paths between symptoms in a liability model (e.g., a relationship between dyssomnia and concentration problems above and beyond depression or internalizing), and the two models can be treated within the same mathematical framework. Additionally, as has been noted, formative models in their strict form assume no measurement error, which may be theoretically untenable (Markus, 2010; McFarland & Malta, 2010) and lead to seemingly unreasonable implications (for example, that measures of a symptom using two different instruments are in fact two different symptoms; Howell et al., 2007a, 2007b).

Finally, although formative models do provide one type of explanation for comorbidity, this explanation is limited in certain respects—for example, describing associations between internalizing symptoms does not explain why internalizing symptoms as a set are more closely associated with one another

than with externalizing symptoms. This would require some metaproperty of the symptom network as an explanation, which would likely resemble a latent variable in some abstract sense.

In general, the greater precision of symptom measurement relative to syndromal assessment has permitted more accurate tests of various comorbidity models. Among liability models, symptom-level analyses have supported the basic conclusions of syndrome-level analyses, with some possible exceptions in how more specific liabilities are understood (e.g., the scope of fear liability). As interest in symptom-level analyses has grown, however, interest in other models, such as the formative models, has grown as well. Although questions have been raised about the utility of formative models, further research is needed to compare them to liability models and understand how to integrate the two types of frameworks.

Depression and Anxiety in the National Study of Daily Experiences

In order to provide examples of these models, and illustrate issues that arise in comorbidity modeling, I compared liability and formative (i.e., network) models of depression and anxiety symptoms in the National Study of Daily Experiences (NSDE; Ryff & Almeida, 2010), which is part of the National Survey of Midlife Development in the United States (MIDUS; Brim et al., 2011; Ryff et al., 2012). The NSDE included measures of depression and anxiety symptoms over a period of several days, allowing for an examination of the causal structure of these symptoms as they unfold over time. To my knowledge, this is the first time liability and formative models of symptom structure have been directly compared. In doing so, I hope to illustrate important considerations in comorbidity modeling, such as the importance of model comparison, parsimony, and generalizability. I also believe that these model comparisons will help illustrate how analysis of comorbidity can help clarify the nature of psychopathology constructs.

The National Study of Daily Experiences: Overview

The NSDE is a subproject of the larger MIDUS study, which is a longitudinal, nationally representative study of psychosocial and health variables in mid-adulthood (Brim et al., 2011; Ryff et al., 2012). MIDUS itself comprises two waves of data collection, 10 years apart, on a nationally representative sample of 7108 adults in the United States, including siblings and twins. The initial wave of MIDUS data (MIDUS I) was collected in 1995–1996; a second wave of data (MIDUS II) was collected approximately 10 years later, in 2004–2006, when participants from the initial wave were recontacted. The NSDE is a substudy conducted in both waves of MIDUS, in which a subsample of participants were interviewed daily about psychological and physical symptoms, stressors, and other daily life events over a period of 8 days. Data on cortisol and other variables were also collected. Here, I focus on the NSDE II, the second wave of data collection, in the primary sample of 1141 participants who were recruited through random digit dialing. Further information on the NSDE is available in Ryff and Almeida (2010); data from it are publicly available through the Inter-university Consortium for Political and Social Research.

Measures and Variables

Although structured clinical interviews were not administered in the NSDE, the interviews did include measures of numerous negative and positive emotional states (Almeida & Kessler, 1998; Mroczek & Kolarz, 1998; Watson, Clark, & Tellegen, 1988), as well as measures of physical and somatic symptoms (King, 2008; Larsen & Kasimatis, 1991). This allowed me to construct indicators of multiple criteria of a Major Depressive Episode (MDE) and of Generalized Anxiety Disorder (GAD). Specifically, I included indicators of poor appetite, lack of concentration, fatigue, restlessness, anxiety, negative self-cognitions (e.g., guilt or worthlessness), depressed mo-od, and irritability. Fatigue and poor appetite were assessed by two independent sets of items asking whether participants experienced fatigue or poor appetite during the day, and if they did, the severity of poor appetite or fatigue (each rated on a 10-point scale, resulting in an 11-point scale for each including those who reported no symptoms). The other criteria were assessed by items asking participants "how much of the time" during the day they felt each emotional or psychological state (rated on a 5-point scale). Anxiety was coded as the average of the "nervous" and "afraid" ratings, and negative self-cognitions were coded as the average of the "worthless" and "ashamed" ratings. Poor concentration was coded as the reverse of the "attentive" rating. Measures were administered using a computer-assisted telephone interview (for further details, see Ryff & Almeida, 2010).

Models

Two types of models were fit to the depression and anxiety symptoms: liability models and

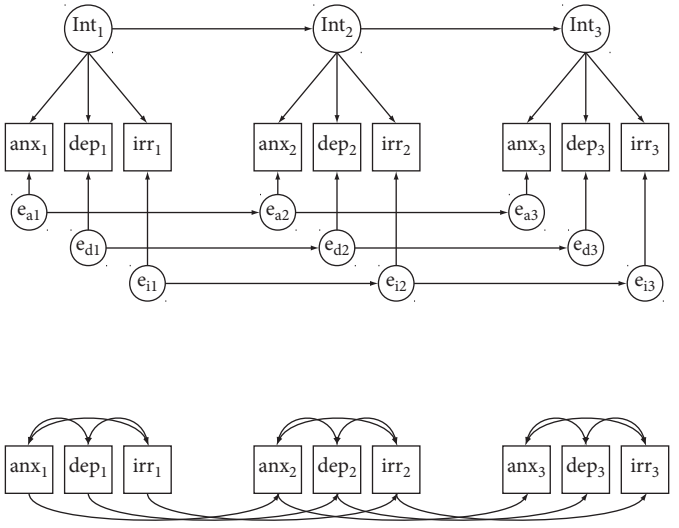

Figure 3.4 Liability (top) and formative (bottom) models of internalizing symptoms in the NSDE. For simplicity, only three criteria and three time points are shown (the models actually include eight criteria at eight time points).

formative models. The basic characteristics of the two models are illustrated in Figure 3.4, with the liability model illustrated in the top, and the formative model illustrated in the bottom. The models are illustrated using only three variables and at three time points, due to space considerations; in the actual models, eight symptom variables were modeled over eight time points. Note also that the relationship between the symptoms and diagnoses are omitted in the models, as the focus in the modeling was on symptoms (for example, the portion of the formative model involving the diagnoses, on the right side, are omitted).

Both types of models comprised two sets of parameters. First, both models comprise paths representing the relationships between the symptoms at each time point, illustrated in the top portion of the figures for both models—internalizing liability in the liability model, and the correlations between the symptoms in the formative model. In the liability model, relationships between the symptoms are explained by an underlying internalizing factor, liability, or construct; in the formative model the symptoms are directly associated with one another. In the liability model, there are autoregressive paths from internalizing at one time point to internalizing at another time point, reflecting the tendency for internalizing on one day to influence internalizing on the next day.

The second set of paths in both models are the residual paths, which represent the unique aspect of each symptom that is not shared with other symptoms. For example, in both models there is assumed to be something unique about irritability that is not shared with other symptoms, under either model. These residual factors are also assumed to influence one another over time, such that irritability per se on one day is assumed to influence irritability on the next day.

In both types of models, parameters were assumed to be the same across days. For example, in the formative model, correlations between symptoms were assumed to be the same across days, and in the liability model, the loadings were assumed to be the same. Similarly, the autoregressive paths were constrained to be the same across days. This assumption is arguably reasonable, as it is difficult to hypothesize a reason why those relationships should change across the week of the study (as opposed to changing across the years of a longitudinal study, for example, where long-term developmental effects might become relevant).

Results and Discussion

Results of the model comparisons are shown in Table 3.1. The table presents the number of freely estimated model parameters, the log-likelihood of the model, and three model selection statistics. Two of them, the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC), are relative model selection statistics, in that they provide information about how the models compare to one another. The other, the root mean square error of approximation (RMSEA) is an absolute model selection statistic, in that it provides information about how each model compares to the data (note that for all three model selection statistics, smaller values are preferable).

PARSIMONY

The model selection statistics in Table 3.1 illustrate the importance of parsimony in comorbidity

Table 3.1 Comparison of Liability and Formative Models of Depressive and Anxiety Symptoms in the NSDE

	k	lnL	AIC	BIC	RMSEA
Liability model	34	–50,688.34	101,444.69	101,614.14	.048
Formative model	52	–50,982.11	102,068.22	102,327.37	.049

Note. Values represent number of model parameters (k), the log-likelihood (lnL), root mean square error of approximation (RMSEA), Akaike's Information Criterion (AIC), and the Bayesian Information Criterion (BIC).

theory and modeling. For example, the RMSEA values for each model suggest that both models fit the data approximately equally closely (.048 for the liability model versus.049 for the formative model), and equally well. Overall, based on RSMEA values alone, one might conclude that both models fit equally well, or possibly that the liability model fits the data slightly more closely.

This conclusion is misleading, however, because the formative model achieves this fit by using one-and-a-half times as many parameters as the liability model. The liability model is much more parsimonious and efficient in this regard, providing a similar level of fit as the formative model but with fewer parameters and less complexity. This greater level of parsimony is reflected in the smaller, more optimal AIC and BIC values for the liability model (AIC = 101,444.69; BIC = 101,614.14) compared to the formative model (AIC = 102,068.22; BIC = 102,327.37).

The greater parsimony of the liability model is important because the statistical literature suggests that conclusions based on more parsimonious models are more likely to generalize (in the sense of cross-validating; Grunwald, 2007; Pitt & Myung, 2002). That is, to some extent, estimates from the formative model will reflect overfitting to a particular sample and will generalize less well and be less replicable in other samples. Although this is also true of the liability model, because the liability model has fewer parameters and is less complex, there is less to overfit with, and conclusions based on it are likely to be more generalizable and replicable.

Although considerations of parsimony are important in any empirical modeling, they become particularly important in comorbidity research. Historically, almost by definition, comorbidity theory and research has tended to focus on explanations of associations between two disorders or conditions at a time (between depression and anxiety, for example, or depression and cancer). Although this is often appropriate and reflects the primary focus of interest (such as with exogenous co-occurrence models), in many cases, the same theories might apply equally to comorbidities between multiple disorders. In such cases, it may be more fruitful to conceptualize comorbidity and its explanations in terms of multimorbidity, or the co-occurrence or covariance of multiple disorders simultaneously (associations between depression, anxiety, phobia, and panic considered simultaneously, for example). Even in cases where only two disorders are involved, specifying theories in terms of multiple indicators (e.g., symptoms or criteria) may be more appropriate. In extending theories formulated for two disorders to multiple disorders or indicators, however, complexity sometimes grows exponentially, and it becomes necessary to consider more parsimonious accounts.

For example, with only two disorders, the final two models of Figure 3.1b (roughly corresponding to liability and formative models) are equally complex and parsimonious. As more disorders are included, however, the final model of Figure 3.1b becomes exponentially more complex, because distinct relationships between each pair of disorders are invoked. The penultimate model in Figure 3.1b, in contrast, increases in complexity less with each additional disorder, because only a single additional path (from the latent variable to the indicator) is added for each additional disorder. In this way, a theory or model that seems reasonably simple with two disorders can quickly become conceptually and statistically complex, perhaps unnecessarily so.

THEORY EXPLICATION IN MODEL COMPARISON

Multimorbidity and symptom models illustrate another, related important consideration in comorbidity theory and research: that theories be elaborated to include as many differentiable features as possible. Traditional philosophies of science generally characterize scientific theory testing in terms of

a process whereby alternate theories are elaborated to include predictions or hypotheses that distinguish one theory from another (e.g., Popper, 1963; van Fraassen, 1980). These theories are then compared in empirical designs that produce data that would be explained differently by the two theories, and the theories are compared using statistical model comparisons. More elaborated theories facilitate this process by providing more, and more distinguishable, tests against alternate theories.

In this regard, comorbidity theories can be compared better when they are made more specific and elaborated in their predictions and hypotheses, in terms of more empirical phenomena that are being explained. Formulating tests of comorbidity theories in terms of multiple disorders that are posited share similar etiologies, or in terms of specific, multiple indicators is more scientifically productive in a sense, because it provides more data points by which those theories can be compared. Somewhat ironically, carrying this reasoning to its extreme, explanations for comorbidity may be more easily identified by abandoning research on comorbidity per se in favor of studies focusing on underlying processes or symptoms of the disorders involved.

This is similar in logic to the endophenotype paradigm (Gottesman & Shields, 1973; Kendler & Neale, 2010), which advocates focusing on underlying processes that are believed to be "closer" to the etiologies of the disorders involved (for example, neuropsychological indicators of perseveration, or negative emotion rather than major depressive disorder per se). From a philosophy of science standpoint, endophenotypes may be most helpful in elucidating comorbidity not because they involve causally primary variables, but because they involve more numerous and more specific variables by which theories can be evaluated. For example, some have questioned the premise of endophenotype theory that some variables are more causally primal, or atomistic in the sense of being less reducible or less complex than other variables (e.g., Flint & Munafo, 2007). However, to the extent that a model is formulated in terms of endophenotypes, which are more precise in terms of hypothesized causal processes, that model then presumably is more precise and specific in terms of how it is formulated and the predictions it makes. The greater specificity or precision of that model then might afford more features whereby it can be empirically evaluated. Endophenotype models, under this reasoning, might not generally be more empirically valid or true, but might be more testable or falsifiable.

Exogenous co-occurrence models of comorbidity, which emphasize the effects of comorbidity rather than its causes, also benefit from more elaborated theory testing. In these cases, including multiple disorders hypothesized to exert the same effect provides multiple tests of the underlying theory. Similarly, formulating models in terms of multiple symptom-level indicators helps provide more specific, nuanced—and therefore more powerful—evaluation of a theory versus alternatives, and helps identify specific pathways that are mediating the effects of comorbidity on outcome.

LIABILITY AND FORMATIVE MODELS OF DEPRESSION AND ANXIETY

Overall, the results in Table 3.1 support a basic liability model for anxiety and depressive symptoms relative to a basic formative model. That is, phenomena such as irritability, depressed mood, anxiety, fatigue, and poor appetite are best conceptualized not as independent but associated experiences, but rather as imperfect indicators of some common underlying state or liability. Although the nature of the underlying liability is unknown, it likely involves negative emotion; according the model, this emotional liability persists somewhat from day to day, imparting continuity in emotional state across time.

It is important to emphasize that under this liability model the symptoms do each have some unique component that is distinct from the underlying liability influencing all depression and anxiety symptoms. Fatigue, for example, is not completely an indicator of emotional liability—it is also an indicator of fatigue per se, independent of anything else—and this unique component persists across time as well. It is reasonable, moreover, to hypothesize that these unique components of each indicator could be related to one another above and beyond any effects of broad internalizing liability. This suggests the possibility of hybrid liability-formative models, where there are direct interindicator relationships in addition to liability effects.

For example, one might hypothesize that in addition to being indicators of internalizing liability, fatigue and attention might be directly related, in that fatigue might directly influence concentration and attention. This model can be specified by allowing the residual components of the fatigue and attention indicators to be directly correlated (i.e., in the notation of Figure 3.4, by adding bidirectional paths between the e_1 fatigue and attention factors, between the e_2 fatigue and attention factors, and

so forth for each day). Fitting this model results in essentially the same RMSEA value as the basic liability model (.048), but improves the AIC (101,391.51) and BIC (101,565.94) values slightly. Although the estimated correlation between fatigue and inattention is small (.120), it is significant (the 95% CI ranges from.069 to .170).

Overall, these results suggest that the processes involved in depression and anxiety symptoms likely combine some features of the liability and formative models. That is, depression and anxiety symptoms share a common internalizing liability, but also may have small direct effects on one another above and beyond this common internalizing liability. In terms of comorbidity, these results suggest that comorbidity between depressive and anxiety disorders likely results mostly from a shared internalizing liability, but also in part from direct relationships between the symptoms that constitute the disorders.

Conclusions

The liability and formative models present remarkably different accounts of the causes of comorbidity: one posits that comorbidity occurs because of a shared etiology, the other posits that comorbidity occurs as an epiphenomenon of definitional criteria directly influencing each other in the absence of any shared etiology. The model comparisons presented here offer some support for aspects of both models, but also illustrate a more general point: delineating causes of comorbidity helps clarify and even redefine the nature of the psychological disorder involved.

Models such as the liability and formative models were originally formulated to explain how two disorders covary. In the process of explaining this covariance, however, the two theories posit accounts that require significant reconceptualizations of what is meant by the disorders involved. Although the two models differ in the nature of this reconceptualization, they both propose that distinct disorders do not necessarily exist in the way they are traditionally understood. In the case of the basic liability model of depressive and anxious comorbidity, for example, depressive disorder and anxiety disorder are in some sense "replaced" by a single internalizing liability; in the case of the basic formative model, depressive disorder and anxiety disorder are "replaced" by dynamically related symptoms.

As evidenced by these analyses, reality is likely to be more nuanced than either a basic liability model or a basic formative model. The processes affecting actual depressive and anxiety symptoms, for example, are likely to resemble both the liability and formative models in some respects. Comparisons of internalizing structural models, moreover, generally indicate that distinct depression and anxiety factors can be identified (Krueger & Markon, 2006; Watson et al., 2007; Markon, 2010), and cannot be entirely replaced by a single internalizing liability. That is, a hierarchy of processes likely exists, including a superordinate internalizing liability that affects a wide spectrum of symptoms (e.g., dysphoria, anhedonia, panic, irritability, and traumatic cognitions), more subordinate liabilities that influence specific types of symptoms (e.g., depression), as well as symptom-level processes per se (e.g., fatigue causing po-or concentration).

Ultimately, attempts to explain comorbidity suggest a significantly different conceptualization of what is meant by "depression" or "anxiety" than what is specified in formal nosologies (for example, the *DSM* or *ICD*; Markon, 2010). That is, in explaining the causes of covariance between two disorders, we redefine those disorders in terms of an alternate set of constructs. In this way, comorbidity research has resulted in a fundamental shift in our understanding of how different forms of psychopathology are structured and the processes involved.

Future Directions

As empirical models of comorbidity continue to evolve and change in focus, a number of important general questions are emerging. One question, for example, is how to flexibly identify causes of association between different forms of psychopathology without making assumptions about the nature of those associations—for example, that the associations are necessarily only mediated by latent liabilities, or are only mediated through reciprocal effects of symptoms on each other. Another question is at what level psychopathology should be examined. Finally, important questions are emerging about how to model interactions between different pathologies, without oversimplifying or drawing spurious conclusions.

Flexible Causal Models of Comorbidity

One emerging issue is how to model comorbidity, or associations between different forms of psychopathology, in a way that is flexible with regard to causal assumptions. Formative models of the sort examined here, for example, allow one to flexibly model reciprocal relationships between observed variables in an exploratory sense.

However, these same formative models do not accommodate unobserved liabilities in the form of latent variables. Conversely, traditional liability models do not allow one to flexibly model latent variables and residual observed variable relationships simultaneously. These models either require specifying the nature of latent variables a priori (for example, using confirmatory factor analysis), or prohibit exploratory identification of residual correlations between observed variables (for example, in an exploratory factor analysis). How to explore comorbidity structures involving mixtures of liability and formative models is currently unclear.

Advances in graphical modeling offer potential solutions to these problems. Graphical models can roughly be thought of as generalizations of, or forms of, structural equation models (Borgelt & Kruse, 2002; Spirtes, Glymour, & Scheines, 2000). Various authors in the graphical modeling literature have explored ways to automatically select different structural models, analogous to automatically searching, comparing, and selecting optimal confirmatory factor models (Silva, Scheines, Glymour, and Spirtes, 2006; Spirtes et al., 2000). For example, rather than specifying different models of how depression and anxiety symptoms are related based on theoretical considerations, one could use an algorithm that automatically generates and compares a wide variety different possible models, and selects the optimal model among them. Spirtes et al. (2000) have advocated for such structural model search algorithms, arguing that they are more rigorous than model comparisons based on theory-driven model comparisons.

These algorithms offer a promising way to explore different accounts of comorbidity and the causal associations that mediate patterns of comorbidity. How to incorporate latent variables of the sort typically encountered in psychopathology research (e.g., multiple correlated latent variables, each with multiple indicators) has proved challenging, however. Kemp and Tenenbaum (2008) provided a framework for identifying optimal structural models, including models with features somewhat analogous to latent variables. Their approach assumes that the structure has some regularity in its features, however, and is limited in how the latent features can be parameterized—it is more similar to cluster analysis than structural equation modeling in many respects. Silva et al. (2006) describe methods for delineating structural models with latent variables that does not have these limitations. They work within a graphical or structural equation modeling framework similar to Spirtes et al. (2000); although their methods are promising, further research is needed to compare these approaches to traditional SEM methods, particularly in terms of their ability to recover generalizable models without capitalizing on chance (see also Danks et al., 2010, for an example of their methods and related discussion of these issues).

Levels of Analysis

Another emerging issue in comorbidity modeling is the question of what level of analysis is most appropriate for understanding associations between different forms of psychopathology. For example, should comorbidity be examined at the level of disorders, symptoms, or underlying liability dimensions? If the latter, in what way should these liabilities be examined? To some extent, these questions reflect broader debates within the field about how to conceptualize mental disorder, but they have important ramifications for understanding what causes covariance and interactions among different forms of disorder.

Approaching revisions to official nosologies, such as the DSM and ICD, have focused attention on general questions about how to define mental disorder. Among these many questions is how to identify the optimal level of analysis for describing and explaining psychopathology. Many have advocated for focus on transdiagnostic constructs (e.g., Nolen-Hoeksema & Watkins, 2011), which are constructs that are relevant to understanding psychopathology across multiple defined disorders. This transdiagnostic paradigm forms the basis for initiatives such as the National Institute of Mental Health's Research Domain Criteria (RDoC; Insel et al., 2010), which seeks to identify a set of working focal constructs for psychopathology research, together with a set of hypothesized processes involved in each construct across different levels of analysis (e.g., genes, cells, neural circuits, or behavior).

Although such efforts are framed as being transdiagnostic, the implied motivation is often not simply to identify constructs that operate across different disorders, but to redefine the focus of psychopathology research. Specifically, the intended change in focus is toward constructs that vary continuously and have a basis in normative neurobehavioral processes (Hyman, 2010; Insel et al., 2010). This has important implications for comorbidity research, if for no other reason than that it implies a shift in

what forms of psychopathology might be considered to be co-occurring or covarying.

Various authors have expressed concern that in the process of redefining focal psychopathology constructs, the level of analysis might shift, intentionally or unintentionally, resulting in the neglect of important etiologies and sequelae of psychopathology. For instance, in the RDoC initiative thus far, although substantial effort has been made to define psychopathology across multiple levels of analysis, certain levels of analysis (e.g., genes, cells, or circuits) have at least implicitly had greater focus relative to other levels of analysis through their absence (e.g., relationships, local environments, or culture; see also Insel et al., 2010). Some have cautioned that attempts to identify optimal levels of analysis in psychopathology, implicitly or explicitly, may lead to neglect of fundamental etiological processes—that it is impossible to fully understand psychopathology at any fixed level of analysis. Kendler (2012a), for instance, using major depressive disorder and alcohol use disorder as examples, reviewed the literature and concluded that, for most forms of psychopathology, focusing on any given level of analysis would be grossly misleading in terms of understanding etiology. In a series of articles (Kendler, 2005, 2012a, 2012b), he has noted that many questions can be asked about the nature of psychopathology, and these questions will dictate the appropriate levels of analysis involved.

Similar issues arise when examining comorbidity per se. Effects of comorbid disorders, for example, may manifest at any number of levels, and the questions that are asked about the nature of those effects will frame the appropriate level of analysis. It is similarly likely that the causes of comorbidity will span multiple different levels of analysis, in different ways for different disorders. At a more fundamental level, evolution in how psychopathology is defined at different levels of analysis will shape study of what comorbid conditions are involved.

Modeling Complex, Multilevel Effects

As the study of comorbidity shifts toward more specific mechanisms, spanning multiple levels of analysis, it is necessary to develop methodologies for studying this phenomenon. These methods ideally will accommodate potential interactions between multiple variables at multiple levels of analysis (e.g., interactions between variables at the level of neural tracts and social environments), involving many different data structures. It is also necessary for these methods to prevent spurious conclusions, such as those that are made on the basis of overfitting to particular samples, or using overly flexible models and designs.

Problems with spurious or ungeneralizable conclusions are not new and not unique to comorbidity research. However, as models of comorbid phenomena become more complex, and as the designs of studies incorporate more features, the opportunities to make inappropriate inferences increase. Various authors have noted how flexibility in study designs and models of resultant data can lead to unreplicable or ungeneralizable conclusions. More flexible models, for example, allow one to capture subtleties of complex effects, but also afford more opportunities to overfit to data (Pitt & Myung, 2002). More flexible designs with more features, similarly, afford more opportunities for multiple testing (Simmons, Nelson, & Simonsohn, 2011).

Nevertheless, developments in psychopathology create important opportunities for the development of new methods for understanding how different forms of psychopathology arise, and how they might interact to affect outcomes. Work in the areas of multilevel modeling (i.e., mixed effects modeling) will continue to grow, accommodating multiple levels of analysis simultaneously. Similarly, work on complex forms of moderation, at the level of observed variables as well as latent constructs (Edwards & Lambert, 2007; Klein & Moosbrugger, 2000) will help clarify how comorbidity arises and influences outcomes. Finally, as these models develop, there will be a need for methods for selecting models and making inferences about them.

Clinical Implications

One implication of the models examined here is that individuals' presenting problems often reflect broad underlying liabilities, liabilities that transcend specific symptoms or even diagnostic boundaries. That is, an individual's depression, fear, or anxiety may reflect broader problems with regulation of negative emotion, patterns of cognitive appraisal, or chronic stressors, rather than depression, fear, or anxiety per se. In this regard, for many clients, it may be more advantageous to focus on identifying broad precipitating factors rather than the specific details of a presenting problem as they manifest at any given time. Many clients are at as great a risk for future problems of the same broad "liability class" as they are the problem they initially present with. For example, a client who initially presents with depression is just as likely to present with anxiety problems later as they are to present with depression again (Fergusson

et al., 2006). In this sense, "relapse" in practice often refers not to the same symptom presentation over and over again, but the same underlying problems over and over. Focusing solely on the specific details of a client's difficulties as they manifest at intake may fail to address the underlying etiologies that increase the risk for other related difficulties.

On the other hand, the models reviewed here also suggest that details do matter. Specific symptoms and situational factors can themselves perpetuate dynamic cycles of difficulties, whereby one crisis feeds another. Intervening at the level of specific symptoms or situational stressors can help ameliorate an individual's difficulties, either by resolving primary problems, or by increasing the client's functioning to a point where broader problems can be more easily addressed. For many clients, the "devil is really in the details," so to speak, and should be a major focus of treatment.

This tension—between treatment of specific situation-response patterns versus broader predisposing factors—is a longstanding issue in the history of clinical psychology and psychiatry. Recurring discussions of "third wave" versus older forms of cognitive-behavioral therapy, for example, have focused in part on this issue (Hayes, 2004), as have related discussions of antecedent versus response-focused intervention (Hofmann & Asmundson, 2008). The models and findings discussed here suggest that this tension is in some ways misguided, as both are likely to be relevant depending on the particular individual and circumstances.

Assessment plays a critical role in this regard: some clients will report difficulties of a relatively specific nature, others difficulties that are broader in scope. Models discussed here suggest that cases where problems are broader in nature do not necessarily reflect a greater number of distinct problems, but might reflect a single underlying process, one that nonetheless impacts a relatively broad range of outcomes. Identifying clients for whom these broader liabilities are critical factors, versus those for whom more specific problems are critical, can be partially addressed through appropriate assessment. It is important in this regard to assess for a range of potential problems, to delineate the boundaries of a client's difficulties. For example, one client presenting with extreme guilt, irritability, and poor concentration may have problems limited to depression in response to a recent stressor; another client presenting with the same difficulties may have problems with negative appraisals more broadly. Assessing such a client's general level of internalizing, along with depression more specifically, would help characterize the breadth of the client's difficulties.

Many similar issues pertaining to the specificity of symptoms have arisen in the *DSM-5* revision process. For example, as noted before, many have suggested that the internalizing symptoms of PTSD are not qualitatively different from those of other forms of internalizing psychopathology (Breslau, Chase, & Anthony, 2002; Yufik & Simms, 2010). This raises the question of whether the trauma criterion of the disorder is necessary for a diagnosis. Similar questions have arisen about the DSM-5 draft criteria for major depression. For example, the bereavement exclusionary criterion has been relaxed, allowing a client to be diagnosed with depression in the presence of a loss. The literature reviewed here would likely support this relaxation, insofar as the difficulties involved in bereavement would resemble that of depression, as well as other internalizing problems. Seen another way, the question of whether or not bereavement is distinct from depression as a disorder is somewhat abstract, with little practical consequence in many cases: the psychological pain of both can be similar and might be treated similarly.

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CHAPTER

4

Examining the Comorbidity Between Depression and the Anxiety Disorders From the Perspective of the Quadripartite Model

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Abstract

Major depression and posttraumatic stress disorder (PTSD) represent heterogeneous combinations of symptoms. Analyses focusing on these distinctive symptom dimensions can play an important role in explicating key diagnostic phenomena such as comorbidity. We review depression and PTSD from the perspective of the quadripartite model, which posits that it is important to consider two quantitative elements when analyzing the properties of symptoms: (a) the magnitude of their general distress component and (b) their level of specificity. Within both disorders, we identified certain symptoms—insomnia and appetite disturbance in the case of depression, dysphoria within PTSD—that both (a) exhibited poor diagnostic specificity and (b) provided little or no incremental information to their respective diagnoses. We therefore argue that deemphasizing these weak and nonspecific indicators and focusing primarily on more specific types of symptoms potentially can improve the diagnosis and assessment of these disorders.

Key Words: major depression, posttraumatic stress disorder, comorbidity, general distress, symptom specificity, dysphoria, diagnosis, assessment

Introduction

In this chapter, we review the historical progression of structural schemes that attempt to model the relation between depression and the anxiety disorders. This topic has been the focus of enormous interest within clinical psychology and psychiatry since the 1980s. Much of the structural work in this area has been stimulated by extensive evidence regarding diagnostic comorbidity. Comorbidity is pervasive within the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM;* American Psychiatric Association, 1980, 1987, 2000), and it is particularly problematic within the mood and anxiety disorders (Clark, Watson, & Reynolds, 1995; Krueger & Markon, 2006; Mineka, Watson, & Clark, 1998; Widiger & Clark, 2000).

For example, Watson (2009) computed weighted mean tetrachoric correlations between *DSM* unipolar mood and anxiety disorder diagnoses across four large national epidemiological samples: the National Comorbidity Survey (Krueger, 1999; N = 8,098, except for posttraumatic stress disorder [PTSD], where N = 5,877) and National Comorbidity Survey Replication (Kessler, Chiu, Demler, & Walters, 2005; N = 3,199) data in the United States; Wave 1 of the Netherlands Mental Health Survey and Incidence Study (W. A. Vollebergh, personal communication, December 15, 2003; N = 7,076) and the Australian National Survey of Mental Health and Well-Being (Slade & Watson, 2006; N = 10,641). Diagnoses of major depression correlated .64 with generalized anxiety disorder (GAD), .57 with obsessive-compulsive disorder (OCD), .56 with PTSD, .55 with panic disorder, .50 with social phobia, .48 with agoraphobia, and .45 with simple/social phobia (see Watson,

2009, for more details). Similarly, tetrachoric correlations between dysthymic disorder and the anxiety disorders ranged from .41 (simple/specific phobia) to .66 (GAD). More generally, most individuals with major depression also meet criteria for a comorbid anxiety disorder and vice versa (see Mineka et al., 1998; Watson, 2005, 2009).

Previous Models

The Two-Factor Affective Model

The "Big Two" dimensions of affect. Why do we see such extensive comorbidity between the mood and anxiety disorders? Watson, Clark, and Carey (1988) originally developed an explanatory model that drew on key findings from the basic mood literature. Extensive evidence establishes the existence of two dominant dimensions of emotional experience: Negative Affect (or Activation) and Positive Affect (or Activation; e.g., Watson & Tellegen, 1985; Watson, Wiese, Vaidya, & Tellegen, 1999). Negative Affect is a general dimension of subjective distress and dissatisfaction. It subsumes a broad range of specific negative emotional states, including fear, anger, sadness, guilt, and disgust. Its emergence in analyses of affect ratings indicates that these various negative emotions significantly co-occur both within and across individuals. Thus an individual who reports feeling anxious and fearful also is likely to report substantial levels of anger, guilt, sadness, and so on. In parallel fashion, the general Positive Affect dimension reflects important co-occurrences among positive mood states; for instance, an individual who reports feeling happy and joyful also will report feeling interested, excited, confident, and alert.

Influence of the general Negative Affect factor. Extrapolating from these data, Watson et al. (1988) argued that this general Negative Affect dimension was largely responsible for the substantial overlap/comorbidity between depression and anxiety. Put differently, this higher order factor produces strong correlations among different types of negative emotion, including sad/depressed affect and fearful/anxious affect.

This idea has received extensive empirical support (see Watson, 2005; Watson, Clark, & Stasik, 2011). For example, Watson, O'Hara, and Stuart (2008) examined the association between measures of depressed mood (e.g., *I felt depressed, I felt like crying*) and anxious mood (e.g., *I felt anxious, I found myself worrying all the time*) in eight different samples (overall N = 3,549). These measures were strongly related in every group; the correlations ranged from .72 (college students) to .85 (older adults), with an overall weighted mean value of .78.

The role of Positive Affect. How, then, can depression and anxiety be distinguished? Findings from the mood literature establish that indicators of the higher order Positive Affect factor consistently correlate negatively with depressed mood and symptomatology and are related more weakly to measures of anxiety (Mineka et al., 1998; Watson & Naragon-Gainey, 2010). One partial exception, however, is that low Positive Affect shows consistent negative associations with social anxiety/social phobia (Kashdan, 2007; Naragon-Gainey, Watson, & Markon, 2009). Low positive affectivity also is consistently linked to negative symptoms of schizophrenia/schizotypy (Watson & Naragon-Gainey, 2010). Thus Watson and Naragon-Gainey (2010) recently concluded that "the reviewed data establish that low levels of positive affect are a distinguishing feature of depression, social anxiety and schizophrenia/schizotypy" (pp. 846–847). They further added that "a more limited range of evidence suggests that indicators of positive affect are more strongly and systematically linked to depression than to these other syndromes" (p. 847).

The two-factor model of affect. Putting these data together, Watson et al. (1988) proposed that low levels of positive affectivity were a specific feature of depression that distinguishes it from the anxiety disorders. Thus, in this *two-factor model*, negative affectivity represents a nonspecific factor common to depression and anxiety, whereas low positive affectivity is a specific factor that is related primarily to depression.

The Tripartite Model

Basic elements of the model. Clark and Watson (1991) subsequently extended this two-factor model by proposing a second specific factor—physiological hyperarousal—that is relatively specific to anxiety. They therefore argued that a *tripartite model* more accurately captures this domain. This model classifies symptoms of anxiety and depression into three basic subgroups. First, many symptoms are strong indicators of the general distress/negative affectivity dimension; this nonspecific group includes both anxious and depressed mood (consistent with the earlier two-factor model), as well as other symptoms (e.g., insomnia, poor concentration) that are prevalent in both the mood and anxiety disorders. In addition, however, each syndrome is characterized by its own cluster of symptoms: somatic tension and hyperarousal (e.g., shortness of breath, dizziness)

are unique to anxiety, whereas anhedonia and low positive affectivity (e.g., loss of interest, feeling that nothing is enjoyable) are specific to depression.

Diagnostic and assessment implications. One important implication of the tripartite model is that differential diagnosis and assessment can be enhanced by focusing more on the specific symptom clusters and deemphasizing nonspecific manifestations of distress/Negative Affect. Watson and Clark (1991) explicitly tested this possibility by creating the Mood and Anxiety Symptom Questionnaire. The questionnaire contains two anxiety scales and two depression scales that vary in their specificity. One member of each scale pair was designed to assess the general distress symptoms traditionally associated with that construct, whereas the other was constructed to tap its unique symptom cluster. Thus, the General Distress: Anxious Symptoms scale includes indicators of anxious mood, as well as other anxiety disorder symptoms that were expected to overlap heavily with depression; in contrast, Anxious Arousal includes various manifestations of somatic hyperarousal. Similarly, the General Distress: Depressive Symptoms scale contains items tapping depressed mood along with other nonspecific symptoms of mood disorder, whereas Anhedonic Depression contains items reflecting anhedonia, disinterest, and anergia (as well as reverse-keyed items assessing Positive Affect).

According to the tripartite model, the two General Distress scales should be highly intercorrelated, whereas the two specific scales should show much better discriminant validity. This prediction has been strongly confirmed in multiple studies. For example, Watson (2000) reported weighted mean correlations between these Mood and Anxiety Symptom Questionnaire scales across eight samples (total N = 3,629). As predicted, the overall correlation between the General Distress: Depression Symptoms and General Distress: Anxiety Symptoms scales was .69 (representing 48% shared variance), whereas the corresponding coefficient between Anhedonic Depression and Anxious Arousal was only .32 (reflecting 10% shared variance). These findings (see also Watson, 2005) highlight the potential benefits of focusing assessment on the unique, specific symptoms within these disorders.

Integrative Hierarchical Model

The basic propositions of the tripartite model have received extensive support (see Mineka et al., 1988; Watson, 2000, 2005). Unfortunately, however, this model suffers from a significant problem in that it fails to account for the heterogeneous nature of the anxiety disorders. This heterogeneity has crucial implications for structural models. Most notably, it means that a single specific factor is insufficient to capture the diversity of symptoms subsumed within these disorders. Indeed, subsequent evidence has established that anxious arousal is not generally characteristic of the anxiety disorders but instead is more specifically related to panic disorder and PTSD (Brown, Chorpita, & Barlow, 1998; Watson, 2009).

To remedy this problem, Mineka et al. (1998) proposed an *integrative hierarchical model* that incorporated elements from both the tripartite model and Barlow's hierarchical organization of the anxiety disorders (see Zinbarg & Barlow, 1996). In this scheme, each individual syndrome is hypothesized to contain both a common and a unique component. Consistent with earlier models, the shared component represents broad individual differences in general distress/negative affectivity; it is a pervasive higher order factor that is common to both the anxiety and mood disorders and primarily is responsible for the overlap/comorbidity between them. In addition, each disorder also includes unique features that differentiate it from all of the others. Thus anxious arousal no longer is viewed as broadly characteristic of the anxiety disorders but instead assumes a more limited role as a specific element in syndromes such as panic disorder.

Mineka et al. (1998) also incorporated an explicitly quantitative component into this integrative scheme. They summarized a range of evidence indicating that the size of these general and specific components differs markedly across disorders. Specifically, major depression and GAD both are distress-laden disorders that clearly contain an enormous amount of this general factor variance; in contrast, most of the other anxiety disorders contain a more modest component of nonspecific negative affectivity (see also Watson, 2005, 2009).

Subsequent evidence has strongly supported basic aspects of the integrative hierarchical model. Kotov, Gamez, Schmidt, and Watson (2010) reported particularly striking meta-analytic evidence for neuroticism, a personality trait that essentially reflects individual differences in negative affectivity (Watson et al., 1999). Kotov et al. compared the mean neuroticism scores of individuals with and without various emotional disorders. Neuroticism displayed large effect sizes (expressed as Cohen's *d;* Cohen, 1988) with every analyzed disorder; for example, *d*s (corrected for unreliability) ranged

from 1.33 to 2.25 for major depression, GAD, PTSD, panic disorder, social phobia, and OCD.

Unfortunately, this model also has run into significant problems. Most notably, the comorbidities among the unipolar mood and anxiety disorders cannot be adequately captured using a single nonspecific factor. That is, the integrative hierarchical model predicts (a) a high level of comorbidity between disorders that have strong components of negative affectivity but (b) weaker overlap between syndromes that are less saturated with this general factor variance. This former proposition has received substantial support in the literature. For example, as noted earlier, Watson (2009) reported a tetrachoric correlation of .64 between major depression and GAD—two disorders that are strongly saturated with general factor variance—across the four large epidemiological samples. The latter prediction has proven to be more problematic, however. For instance, Watson (2009) obtained a correlation of .61 between social phobia and agoraphobia—two disorders containing a lesser component of general distress—in these same samples (see also Watson, 2005).

The Quadripartite Model

Basic elements of the model. These comorbidity data demonstrated the need for further structural refinements. Watson (2009) therefore articulated a *quadripartite model* that focuses on specific symptom dimensions within the mood and anxiety disorders (e.g., specific symptoms within PTSD). This new scheme represents a synthesis of the earlier tripartite and integrative hierarchical models. It adopts the explicit symptom focus of the tripartite model but—similar to the integrative hierarchical model—uses the *DSM* mood and anxiety disorders as its organizing framework. This explicit link to the *DSM* eliminates the most notable limitation of the tripartite model by capturing the full range of content within the *DSM-IV* anxiety disorders.

In addition, this new scheme incorporates the explicit quantitative focus of the integrative hierarchical model. This quantitative focus has two interrelated elements. First, the tripartite model simply classifies anxiety and depression symptoms as either specific (e.g., anhedonia and anxious arousal) or nonspecific (e.g., anxious and depressed mood). In contrast, Mineka et al. (1998) adopted a more nuanced quantitative approach in the integrative hierarchical model, arguing that "symptom specificity must be viewed in relative rather than absolute terms…we need to move toward more complex, multilevel hierarchical models in which groups of symptoms are classified at varying levels of specificity" (p. 398).

Second, as discussed earlier, Mineka et al. (1998) demonstrated that the size of the general distress/negative affectivity component differs markedly across symptoms and disorders. For example, major depression, dysthymic disorder, and GAD all are heavily saturated with this general distress variance, whereas disorders such as agoraphobia and specific phobia contain a more limited component of negative affectivity (see also Watson, Gamez, & Simms, 2005).

Thus from the perspective of the quadripartite model, we need to consider two quantitative elements when analyzing the properties of symptoms: (a) the level of specificity and (b) the magnitude of the general distress variance. Clearly, these two symptom properties are not independent of one another. Most notably, symptoms that are heavily saturated with general distress/negative affectivity—such as depressed and anxious mood—will be strongly correlated and, therefore, can be expected to show a reduced level of specificity (Watson, 2005; Watson et al., 2007; Watson et al., 2008).

Nevertheless, it is important to consider these two quantitative elements separately as distinct properties of symptoms. Although they are most accurately viewed as quantitative dimensions, for the sake of convenience we can use these elements to create an organizing 2 × 2 classification scheme, which produces four basic types of symptoms:

(1) high distress symptoms with limited specificity
(2) high distress symptoms with greater specificity
(3) low distress symptoms with greater specificity
(4) low distress symptoms with limited specificity.

It is the existence of this fourth group that clearly establishes the quasi-independence of the specificity and distress elements of the model and that most sharply differentiates this new scheme from the tripartite model (in which nonspecific symptoms were assumed to have a strong component of general distress): From the perspective of the quadripartite model, even symptoms that have a relatively weak distress component can show little or no specificity.

Diagnostic and assessment implications. This final group of symptoms has important implications for differential diagnosis and assessment, particularly with regard to depression. As noted earlier, we can enhance differential diagnosis and assessment by

focusing greater attention on the specific symptoms contained in the second and third groups. In addition, even though the distress-laden symptoms of the first group can create significant problems with regard to differential diagnosis and discriminant validity, they obviously are enormously important and, in fact, lie at the very heart of the mood and anxiety disorders (Watson, 2005; Watson et al., 2007; Watson et al., 2008). Consequently, the symptoms included in the first three groups all play an essential role in the diagnosis and assessment of the mood and anxiety disorders.

But how essential are the low distress, limited specificity symptoms of the fourth group? We address this issue in subsequent analyses, using the quadripartite model as an organizing framework for understanding the comorbidity between depression and the anxiety disorders. We focus primarily on the symptom dimensions within major depression but then consider PTSD symptoms more briefly. In each case, we examine two basic questions. The first question concerns the central issue of specificity/discriminant validity: To what extent do these symptoms display specificity to their respective disorders, as opposed to being more broadly and nonspecifically related to internalizing psychopathology (e.g., is insomnia specific to depression)? The second question involves the key issue of criterion/incremental validity: How important are these symptoms to their respective diagnoses (e.g., does insomnia make a significant incremental contribution to diagnoses of depression)?

Considered together, the results of these analyses potentially have important diagnostic and assessment implications. We argue that symptoms that both (a) display poor specificity and (b) provide little incremental diagnostic information are of questionable validity and, therefore, are prime candidates for elimination. Put differently, the problem of comorbidity can be lessened by removing—or at least deemphasizing—poorly functioning symptoms.

Depression Symptoms

A Measurement Model for Depression

The IDAS Depression Scales. Depression symptoms are characterized by a strong general factor (e.g., Beck, Steer, & Garbin, 1988; Watson et al., 2007), a point we return to shortly. Consequently, these symptoms typically are summed into a single overall score. Nevertheless, Watson et al. (2007) were able to differentiate several meaningful and replicable symptom dimensions within depression; scales assessing these dimensions were included in the Inventory of Depression and Anxiety Symptoms (IDAS).

In creating the initial IDAS item pool, Watson et al. (2007) included multiple markers to define all of the symptom dimensions that potentially could emerge in structural analyses. To ensure that sufficient markers were included for each potential dimension, the candidate items were rationally organized into *homogeneous item composites* (Hogan, 1983), or HICs. The original IDAS item pool contained 13 HICs targeting symptoms that are broadly relevant to depression, as well as 7 HICs assessing various anxiety-related symptoms. Nine HICs corresponded to the basic symptom criteria for major depression in the *DSM* (fourth edition *[DSM-IV*]; American Psychiatric Association, 2000): depressed mood, loss of interest or pleasure, appetite disturbance, sleep disturbance, psychomotor problems, fatigue/anergia, feelings of worthlessness and guilt, cognitive problems, and suicidal ideation. The four remaining HICs tapped hopelessness/pessimism (this targeted the hopelessness subtype of depression; Abramson, Metalsky, & Alloy, 1989), the symptom features of melancholic depression, angry/irritable mood (which can be an alternative expression of depressed mood in children and adolescents), and markers of high energy and Positive Affect (which are specifically related to depression; Clark & Watson, 1991; Mineka et al., 1998).

The 169 items contained in these 20 HICs were administered to large samples of college students, psychiatric patients, and community adults (Watson et al., 2007, Study 2). Data from these three samples were subjected to separate series of principal factor analyses. These analyses yielded several important findings that helped to clarify the structure of depression symptoms. First, as expected, these analyses revealed a very large, nonspecific factor that was defined by the core affective/cognitive symptoms of both depression and anxiety. It is particularly noteworthy that items assessing five of the nine *DSM-IV* symptom criteria for a major depressive episode—Criterion 1 (depressed mood), Criterion 2 (anhedonia/loss of interest), Criterion 5 (psychomotor problems), Criterion 7 (worthlessness/guilt), and Criterion 8 (cognitive problems)—were very highly interrelated and defined a single common factor (see also Watson, 2009). Items assessing anxious mood and worry also were strong markers of this general dimension. Overall, therefore, we again see evidence of a broad factor that is strongly saturated with general distress/negative affectivity and that lies at the very core of the

mood and anxiety disorders: It subsumes more than half of the *DSM-IV* symptom criteria for a major depressive episode, as well as the central features of GAD. To capture the content encompassed within this broad factor, Watson et al. (2007) created the 10-item IDAS Dysphoria scale, which contains symptoms assessing depressed mood, loss of interest, worry, worthlessness, guilt, hopelessness, cognitive disturbance, and psychomotor problems.

Beyond this general factor, however, several specific symptom dimensions consistently emerged in these structural analyses and were used to create corresponding IDAS scales. Five of these scales assess classic manifestations of depression. The IDAS Suicidality scale essentially represents *DSM-IV* Criterion 9 for a major depressive episode, the Insomnia scale taps the corresponding portion of Criterion 4 (sleep disturbance), and Appetite Loss and Appetite Gain jointly define Criterion 3 (appetite disturbance). The final scale—Lassitude—includes content related to both fatigue/anergia (Criterion 6) and the hypersomnia portion of Criterion 4. More generally, analyses of the IDAS item pool consistently showed that hypersomnia symptoms actually correlate much more strongly with fatigue/anergia (*r*s ranged from .61 to .69 across the three samples) than with insomnia (*r*s ranged from only .14 to .26). Thus, these results (see also Koffel & Watson, 2009) suggest that the diagnosis of depression potentially could be improved by moving hypersomnia from Criterion 4 to Criterion 6.

Consequently, six IDAS scales—Dysphoria, Insomnia, Lassitude, Suicidality, Appetite Loss, and Appetite Gain—jointly capture all of the symptom content included in the *DSM-IV* diagnostic criteria for a major depressive episode. Watson (2009) examined the relations among these depression scales (see also Watson et al., 2007, 2012). Supporting a basic tenet of the quadripartite model, the specific symptom scales correlated quite differently with Dysphoria and clearly contained different amounts of general distress variance (see Watson, 2009, Table 4.6). That is, Dysphoria correlated strongly with Lassitude (r = .63) and Suicidality (r = .62), more moderately with Insomnia (r = .53) and Appetite Loss (r = .44), and relatively weakly with Appetite Gain (r = .27). It is noteworthy, moreover, that clinicians' ratings showed the same differential pattern. Thus depression symptoms clearly vary in the strength of their general distress components. Based on the logic of the earlier tripartite model, one would expect those symptoms that are less strongly saturated with general distress variance (e.g., insomnia, appetite loss) to show the greatest specificity and to be the purest indicators of depression. From the perspective of the quadripartite model, however, this is not necessarily the case: Specificity represents a separate quantitative element that is distinct from the magnitude of the general distress variance.

We examine the specificity and incremental predictive power of these six IDAS depression scales in subsequent analyses. We also report results for the IDAS Well-Being scale, which contains high Positive Affect items that show considerable specificity to depression (Mineka et al., 1998; Watson, 2009; Watson et al., 2011; Watson & Naragon-Gainey, 2010).

It also is important to establish that these findings generalize across measures and methods. Consequently, in addition to reporting results based on the self-report IDAS scales, we present findings based on two parallel interview measures: the Clinician Rating version of the IDAS (IDAS-CR; Watson, 2009; Watson, O'Hara, Chmielewski, et al., 2008) and the Interview for Mood and Anxiety Symptoms (IMAS; Gamez, Kotov, & Watson, 2010; Watson et al., 2007). Before proceeding to our main analyses, we examine the convergent and discriminant validity of these measures to establish that (a) they assess the same basic constructs and (b) depression symptoms can be meaningfully distinguished from one another across methods.

IDAS-CR analyses. The IDAS-CR consists of a series of single-item ratings representing each of the IDAS scales. Each rating is made on a 3-point scale (*absent, subthreshold, present*). To rate each symptom, the clinicians asks a standard initial probe question, as well as several standard follow up questions. Watson, O'Hara, Chmielewski, et al. (2008) established strong interrater reliability for these ratings in both students (intraclass correlations ranged from .65 to .95, median = .87) and patients (range = .74 to .99, median = .89).

We present correlations between the IDAS scales and IDAS-CR ratings in 804 outpatients (Table 4.1) and 522 University of Iowa students (Table 4.2) in the form of a heteromethod block (Campbell & Fiske, 1959); it should be noted that these are augmented versions of the results reported previously in Watson, O'Hara, Chmielewski, et al. (2008), using additional data from samples described in Watson et al. (2012). Looking first at convergent validity, all of the IDAS scales were significantly related to their IDAS-CR counterparts in both samples. Convergent correlations in the patient sample

Table 4.1 Correlations Between the IDAS Scales and IDAS-CR Ratings (Patient Sample)

	IDAS-CR Rating						
IDAS Scale	1	2	3	4	5	6	7
1. Appetite Loss	***.71***	.22	.27	–.32	.21	.27	–.24
2. Suicidality	.22	***.67***	.37	.06	.25	.14	–.39
3. Dysphoria	.29	.42	***.60***	.10	.43	.25	–.48
4. Appetite Gain	–.30	.08	.13	***.60***	.19	.00	–.01
5. Lassitude	.14	.22	.37	.16	***.59***	.13	–.25
6. Insomnia	.25	.19	.27	.02	.28	***.59***	–.24
7. Well-Being	–.15	–.31	–.43	–.02	–.29	–.11	***.54***

Note. N = 804. Convergent correlations are highlighted. Correlations ≥ |.08| are significant at $p < .05$. IDAS = Inventory of Depression and Anxiety Symptoms; IDAS-CR = Clinician Rating version of the IDAS. These results are based on a combined sample that includes data from both (a) the patient group described in Watson, O'Hara, Chmielewski, et al. (2008) and (b) Patient Sample 2 from Watson et al. (2012).

ranged from .54 (Well-Being) to .71 (Appetite Loss), with a mean coefficient of .62; parallel values in the student data ranged from .39 (Well-Being) to .62 (Appetite Loss), with a mean coefficient of .53. These results are particularly impressive given that the IDAS-CR consists of a series of single ratings. Thus, consistent with previous research (e.g., Beck et al., 1988; Clark & Watson, 1991; Watson et al., 2007), these data demonstrate substantial associations between self-report and interview-based symptom measures.

We turn now to discriminant validity. A classic test of discriminant validity is that each of the convergent correlations should be higher than any of the other values in its row or column of the heteromethod block (Campbell & Fiske, 1959). With one exception (Well-Being in the student sample), the scales all met this criterion. We further quantified these relations by conducting significance tests (using the Williams modification of the Hotelling test for two correlations involving a common variable; see Kenny, 1987), comparing these convergent

Table 4.2 Correlations Between the IDAS Scales and IDAS-CR Ratings (Student Sample)

	IDAS-CR Rating						
IDAS Scale	1	2	3	4	5	6	7
1. Appetite Loss	***.62***	.25	.13	.11	–.14	.07	–.12
2. Dysphoria	.20	***.61***	.46	.31	.20	.21	–.28
3. Lassitude	.14	.44	***.55***	.22	.22	.17	–.24
4. Insomnia	.18	.29	.33	***.51***	.09	.12	–.15
5. Appetite Gain	–.12	.23	.26	.08	***.51***	.16	–.08
6. Suicidality	.12	.31	.24	.18	.12	***.48***	–.22
7. Well-Being	–.12	–.43	–.32	–.22	–.10	–.18	***.39***

Note. N = 522. Convergent correlations are highlighted. Correlations ≥ |.10| are significant at $p < .05$. IDAS = Inventory of Depression and Anxiety Symptoms; IDAS-CR = Clinician Rating version of the IDAS. These results are based on a combined sample that includes data from both (a) the student group described in Watson, O'Hara, Chmielewski, et al. (2008) and (b) Student Sample 3 from Watson et al. (2012).

Table 4.3 Correlations Between the IDAS and IMAS Scales

	IMAS Scale				
IDAS Scale	**1**	**2**	**3**	**4**	**5**
1. Insomnia	***.74***	.27	.40	.43	.39
2. Suicidality	.21	***.71***	.20	.45	.30
3. Appetite Loss	.31	.24	***.70***	.32	.35
4. Dysphoria	.37	.45	.35	***.64***	.57
5. Lassitude	.14	.26	.24	.44	***.61***

Note. $N = 390$. Convergent correlations are highlighted. All correlations are significant at $p < .01$. IDAS = Inventory of Depression and Anxiety Symptoms; IMAS = Interview for Mood and Anxiety Symptoms. These results are based on Patient Sample 3 from Watson et al. (2012).

correlations to each of the 12 discriminant coefficients in the same row or column of the block; this yielded a total of 84 tests of discriminant validity across these seven symptom dimensions in each sample. Overall, 166 of these 168 comparisons (98.8%) were significant ($p < .05$, one-tailed), which offers strong evidence of discriminant validity. The two exceptions were that the convergent coefficient for Well-Being ($r = .39$) did not significantly exceed the discriminant correlations between (a) IDAS Well-Being and IDAS-CR Dysphoria and (b) IDAS Well-Being and IDAS-CR Lassitude in the student data.

IMAS analyses. We report IMAS data on 390 outpatients (for a description of this sample, see Watson et al., 2012). The IMAS assesses current (i.e., past month) symptoms; individual items are scored on a 3-point rating scale (*absent, subthreshold, above threshold*). Items were derived from the mood and anxiety disorder modules of the Composite International Diagnostic Interview (Kessler & Üstün, 2004) and were designed to cover all *DSM-IV* mood and anxiety disorder symptom criteria. Based on data from prior studies (Gamez et al., 2010; Watson et al., 2007), the IMAS was revised to improve its symptom coverage. The revised version includes five-item measures of Dysphoria and Lassitude, four-item Insomnia and Suicidality scales, and a three-item measure of Appetite Loss.

Extensively trained lay interviewers administered the IMAS. All interviews were recorded; a randomly selected interviewer rescored 34 tapes. Interrater reliability consistently was excellent, with intraclass correlation coefficients ranging from .97 to .99 across the various scales (see Watson et al., 2012).

Table 4.3 presents correlations between the IDAS and IMAS scales in the form of a heteromethod block. We again see strong evidence of convergent validity, with correlations ranging from .61 (Lassitude) to .74 (Insomnia; mean $r = .68$). With regard to discriminant validity, we again conducted significance tests comparing each of the convergent correlations to all of the other values in its row or column of the heteromethod block. The results indicated that 39 of the 40 comparisons (97.5%) were significant ($p < .05$, one-tailed); the sole exception was that the convergent correlation for Lassitude ($r = .61$) was not significantly higher than the discriminant correlation between IDAS Dysphoria and IMAS Lassitude ($r = .57$).

Overall, these data offer strong evidence of convergent and discriminant validity. All of the convergent correlations were significant and at least moderate in magnitude, with mean coefficients of .53 (IDAS-CR student analyses), .62 (IDAS-CR patient analyses), and .68 (IMAS analyses). The scales also generally showed excellent discriminant validity; indeed, 205 of the 208 individual comparisons (98.6%) were significant ($p < .05$, one-tailed) across these analyses. Thus our data demonstrate that specific depression symptoms—such as lassitude, insomnia, suicidality, and appetite loss—can be distinguished from one another across methods.

Specificity to Depression

Relations with the Beck Inventories. How specific are these symptoms to depression? This issue can be analyzed in a number of different ways and from several different perspectives. For example, Watson (2009) examined how the IDAS scales correlated with the Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996) and the Beck Anxiety Inventory (BAI; Beck & Steer, 1990) in two large samples (combined $N = 2{,}783$). Well-Being showed the most impressive specificity in these data, correlating much more strongly with the BDI-II (mean $r = –.56$) than with the BAI (mean $r = –.32$). Lassitude (mean rs = .62 and .50, respectively), Suicidality (mean rs = .58 and .47, respectively), and Dysphoria (mean rs = .81 and .71, respectively) also displayed a reasonable level of specificity in these data.

In contrast, the three remaining scales—Insomnia, Appetite Loss, and Appetite Gain—showed much poorer specificity (see Watson, 2009, Table 4.7). Indeed, Insomnia (mean rs = .50 and .47, respectively) and Appetite Loss (mean rs = .39 and .39, respectively) had virtually identical correlations with the two instruments. These results are

particularly striking when one considers that these IDAS scales actually share overlapping item content with the BDI-II but not the BAI.

Diagnostic specificity. In the discussion that follows, we concentrate on the key issue of diagnostic specificity, that is, whether these symptoms are more strongly related to major depression than to anxiety disorders (for earlier examinations of this issue, see Watson, 2009; Watson, O'Hara, Chmielewski, et al., 2008). Although the available evidence on this topic is quite limited, there is reason to question the diagnostic specificity of some depression symptoms. For instance, Benazzi (2006) examined the prevalence of depression symptoms in samples of patients diagnosed with bipolar-II (BP-II) disorder and major depression; his results indicated that several symptoms (as assessed by the Structured Clinical Interview for *DSM-IV* [SCID-IV]; First, Spitzer, Gibbon, & Williams, 1997) showed poor diagnostic specificity. More specifically, symptoms of weight gain, increased eating, hypersomnia, psychomotor agitation, worthlessness, and poor concentration were actually significantly more common in BP-II patients than in those with major depression. Such an overlap in symptom presentation poses problems for discriminating between diagnoses and could lead to the underdiagnosis or misdiagnosis of BP-II (Benazzi, 2006).

It is noteworthy, moreover, that several of the symptom criteria for major depression are also part of the criterion sets for other mental disorders. For example, insomnia is one of the Criterion D symptoms of PTSD, and difficulty concentrating is included in the diagnostic criteria for both PTSD and GAD. In a related vein, Carney, Ulmer, Edinger, Krystal, and Knauss (2009) noted that self-report measures of depression include symptoms that are also essential features of primary insomnia (e.g., insomnia, mood disturbance, irritability, fatigue, impaired concentration, and motivation/anergia). Accordingly, Carney et al. (2009) assessed the accuracy of the BDI-II in detecting major depression in patients known to meet diagnostic criteria for insomnia. They found that several BDI-II items failed to differentiate (a) those with insomnia from (b) those with insomnia and comorbid depression. More specifically, there were no significant differences between groups on insomnia, irritability, suicidal ideation, increased appetite, decreased concentration, fatigue, decreased libido, and self-critical and punishment-related thoughts. The items that did successfully demonstrate group differences included those related to depressed mood, pessimism, past failure, anhedonia, guilt, self-dislike, crying, agitation, indecision, worthlessness, energy, hypersomnia, and loss of appetite. Thus, on the basis of this limited evidence, it appears that some symptoms are better, purer indicators of depression than are others.

To examine this issue more fully, we report six analyses of diagnostic specificity that enable us to evaluate the robustness of these patterns across methods, measures, and populations. To obtain current *DSM-IV* diagnoses, all participants were interviewed by masters' level psychologists using the SCID-IV (for interrater reliability data, see Watson, O'Hara, Chmielewski, et al., 2008). To examine diagnostic specificity, we computed polychoric correlations between depression symptom measures and various *DSM-IV* mood and anxiety disorder diagnoses. Polychoric correlations estimate the associations between normally distributed latent continuous variables that are presumed to underlie observed scores (Flora & Curran, 2004; Schmukle & Egloff, 2009; Watson & Tellegen, 1999). They retain the relative rank order information provided by Pearson correlations (i.e., the same scales will be relatively strong—or weak—predictors of particular diagnoses) but are unaffected by differences in prevalence rates, thereby facilitating cross-diagnosis comparisons. Diagnoses were scored as zero = *absent*, 1 = *present*, so that positive correlations indicate that higher scores on a scale are associated with an increased likelihood of receiving the diagnosis.

In the first three analyses, we present polychoric correlations between the IDAS (N = 894; see Table 4.4), IDAS-CR (N = 604; see Table 4.5), and IMAS (N = 293; see Table 4.6) depression scales and eight *DSM-IV* mood and anxiety disorder diagnoses (major depression, GAD, PTSD, panic disorder, agoraphobia, social phobia, specific phobia, OCD) in outpatient samples. The fourth analysis examines how the IDAS scales correlate with diagnoses of (a) major depression and (b) GAD in a sample of 337 postpartum women (see Table 4.7). The final two analyses (see Table 4.8) consider how the IDAS scales (N = 307) and IDAS-CR ratings (N = 303) correlate with diagnoses of (a) major depression and (b) any anxiety disorder in a college student sample (for more details regarding these samples, see Watson et al., 2007; Watson, O'Hara, Chmielewski, et al., 2008; Watson et al., 2012).

What do these analyses tell us about the specificity of depression symptoms? In order to make sense

Table 4.4 Polychoric Correlations Between the IDAS Scales and *DSM-IV* Diagnoses (Patient Sample)

IDAS Scale	MDD	GAD	PTSD	Panic	Agora	Social Phobia	Specific Phobia	OCD
Dysphoria	***.73***	***.46***	***.40***	***.43***	.32	.27	.19	.24
Lassitude	***.50***	.27	.30	.26	.21	.15	.11	.12
Suicidality	***.51***	.24	.28	.24	.19	.16	.09	.18
Insomnia	***.40***	.29	.39	.32	.23	.19	.21	.24
Appetite Loss	.38	.18	.39	.33	.19	.16	.12	.13
Appetite Gain	.11	.04	.05	–.07	.01	.02	.09	.06
Well-Being	–***.49***	–.21	–.17	–.22	–.24	–.15	–.04	–.17

Note. N = 894. Correlations ≥ |.40| are highlighted. IDAS = Inventory of Depression and Anxiety Symptoms; *DSM-IV* = *Diagnostic and Statistical Manual of Mental Disorders* (fourth edition); MDD = major depression; GAD = generalized anxiety disorder; PTSD = posttraumatic stress disorder; Agora = agoraphobia; OCD = obsessive-compulsive disorder. These results are based on a combined sample that includes data from both (a) the patient group described in Watson, O'Hara, Chmielewski, et al. (2008) and (b) Patient Sample 3 from Watson et al. (2012).

of these complex results, we provide brief summaries of the results for each symptom dimension.

Dysphoria. Replicating and extending the results of Watson (2009), the dysphoria measures showed both (a) the strongest overall association with major depression and (b) impressive diagnostic specificity in these analyses. Specifically, they had the strongest correlation with major depression in five of six analyses (*r*s ranged from .54 to .83) and in every case correlated more strongly with depression than with any other disorder. To quantify these effects further, we computed weighted mean correlations across all of these analyses. Overall, the dysphoria measures had a mean correlation of .69 with major depression; in marked contrast, their average correlations with specific anxiety disorder diagnoses were only .44 (GAD), .40 (panic disorder), .39 (PTSD), .29 (agoraphobia), .26 (social phobia), .24 (OCD), and .18 (specific phobia). Thus, consistent with the findings of Watson (2009), we again see evidence that symptoms containing a very strong general distress component still can display considerable specificity.

Lassitude. Indicators of lassitude also were strongly related to depression (*r*s ranged from .50 to

Table 4.5 Polychoric Correlations Between IDAS-CR Ratings and *DSM-IV* Diagnoses (Patient Sample)

IDAS-CR Rating	MDD	GAD	PTSD	Panic	Agora	Social Phobia	Specific Phobia	OCD
Dysphoria	***.66***	***.44***	.35	***.48***	.38	.30	.19	.32
Lassitude	***.56***	.27	.30	***.41***	.37	.30	.16	***.42***
Suicidality	***.50***	.24	.21	.28	.21	.20	.09	.26
Insomnia	.29	.24	.30	.33	.24	.18	.02	.18
Appetite Loss	.33	.23	.32	.32	.05	.19	.06	.10
Appetite Gain	.23	–.01	.02	–.12	.01	–.06	.08	.07
Well-Being	–***.54***	–.26	–.25	–.39	–.38	–.15	–.06	–.24

Note. N = 604. Correlations ≥ |.40| are highlighted. IDAS-CR = Clinician Rating version of the IDAS; *DSM-IV* = *Diagnostic and Statistical Manual of Mental Disorders* (fourth edition); MDD = major depression; GAD = generalized anxiety disorder; PTSD = posttraumatic stress disorder; Agora = agoraphobia; OCD = obsessive-compulsive disorder. These results are based on the patient sample described in Watson, O'Hara, Chmielewski, et al. (2008).

Table 4.6 Polychoric Correlations Between the IMAS Scales and *DSM-IV* Diagnoses (Patient Sample)

IMAS Scale	MDD	GAD	PTSD	Panic	Agora	Social Phobia	Specific Phobia	OCD
Dysphoria	***.54***	.25	***.42***	.16	.04	.17	.14	.08
Lassitude	***.61***	.28	.30	.33	.23	.16	.16	–.01
Suicidality	.34	.14	.22	.13	.07	.09	.20	.19
Insomnia	.31	.09	.26	.21	.20	.18	.28	.15
Appetite Loss	***.43***	.09	***.48***	.27	.28	.08	.20	.25

Note. N = 293. Correlations ≥ |.40| are highlighted. IMAS = Interview for Mood and Anxiety Symptoms; *DSM-IV = Diagnostic and Statistical Manual of Mental Disorders* (fourth edition); MDD = major depression; GAD = generalized anxiety disorder; PTSD = posttraumatic stress disorder; Agora = agoraphobia; OCD = obsessive-compulsive disorder. These results are based on Patient Sample 3 from Watson et al. (2012).

.61) and displayed impressive diagnostic specificity in these analyses. Lassitude was the strongest predictor of depression in the IMAS data (see Table 4.6) and correlated more strongly with depression than with any other disorder in all six analyses. Overall, lassitude symptoms had a weighted mean correlation of .55 with major depression, whereas their average correlations with specific anxiety diagnoses ranged from only .14 (specific phobia) to .32 (panic disorder). These findings are consistent with the results of Watson (2009) and indicate that lassitude is a strong and specific symptom of depression.

Well-Being. Consistent with the tripartite and integrative hierarchical models, the well-being measures were substantially related to major depression (*r*s ranged from –.42 to –.56) and also showed considerable specificity in these analyses, particularly in the patient data. Overall, they had a weighted mean correlation of –.50 with major depression; in contrast, their average associations with specific anxiety disorder diagnoses ranged from only –.05 (specific phobia) to –.30 (agoraphobia).

Suicidality. Suicidality symptoms displayed impressive specificity in these data; in all six analyses, they correlated more strongly with major depression (*r*s ranged from .34 to .59) than with any other disorder. Overall, these scales had a mean

Table 4.7 Polychoric Correlations Between the IDAS Scales and *DSM-IV* Diagnoses (Postpartum Sample)

IDAS Scale	MDD	GAD
Dysphoria	***.66***	***.56***
Lassitude	***.57***	***.46***
Suicidality	***.48***	.29
Insomnia	***.42***	***.51***
Appetite Loss	.37	.12
Appetite Gain	.15	.28
Well-Being	***–.44***	***–.43***

Note. N = 337. Correlations ≥ |.40| are highlighted. IDAS = Inventory of Depression and Anxiety Symptoms; *DSM-IV = Diagnostic and Statistical Manual of Mental Disorders* (fourth edition); MDD = major depression; GAD = generalized anxiety disorder. These results are based on an expanded version of the postpartum sample described in Watson et al. (2007).

Table 4.8 Polychoric Correlations Between the IDAS Scales, IDAS-CR Ratings, and *DSM-IV* Diagnoses (Student Sample)

	IDAS		IDAS-CR	
Symptom	MDD	Any AD	MDD	Any AD
Dysphoria	***.83***	***.61***	***.69***	***.51***
Lassitude	***.56***	.35	***.58***	***.44***
Suicidality	***.59***	***.49***	***.50***	.33
Insomnia	.39	.24	.30	.25
Appetite Loss	.33	.14	.19	.27
Appetite Gain	.19	.10	.21	.23
Well-Being	***–.56***	–.36	***–.42***	***–.43***

Note. N = 307 (IDAS analyses), 303 (IDAS-CR analyses). Correlations ≥ |.40| are highlighted. IDAS = Inventory of Depression and Anxiety Symptoms; IDAS-CR = Clinician Rating version of the IDAS; *DSM-IV = Diagnostic and Statistical Manual of Mental Disorders* (fourth edition); MDD = major depression; AD = anxiety disorder. These results are based on the student sample described in Watson, O'Hara, Chmielewski, et al. (2008).

correlation of .49 with major depression, whereas their average correlations with specific anxiety disorder diagnoses ranged from only .11 (specific phobia) to .25 (PTSD). These results are consistent with the findings of Watson (2009) and indicate that suicidality is a relatively strong and specific symptom of depression.

Insomnia. In contrast, insomnia measures were more modestly related to major depression (*r*s ranged from .29 to .42) and showed weak, inconsistent evidence of diagnostic specificity. Overall, the insomnia scales had very similar mean correlations with major depression (.36), PTSD (.34), panic disorder (.31), and GAD (.28). Thus, consistent with the results of Watson (2009), these findings indicate that insomnia is a relatively weak and nonspecific indicator of depression.

Appetite loss. Findings for the appetite loss scales were very similar to those for insomnia: These measures had relatively weak correlations with major depression (*r*s ranged from .19 to .43) and showed little specificity. Overall, symptoms of appetite loss had a mean correlation of only .35 with major depression; they correlated very similarly with panic disorder (average $r = .32$) and actually had a slightly stronger association with PTSD (mean $r = .38$). Therefore, similar to insomnia, appetite loss also is a relatively weak and nonspecific symptom of depression.

Appetite gain. Consistent with previous results (see Watson, 2009; Watson et al., 2007; Watson, O'Hara, Chmielewski, et al., 2008), the appetite gain scales had the weakest overall associations with major depression (*r*s ranged from .11 to .23, mean $r = .17$). Their relations with the anxiety disorders were inconsistent across analyses but tended to be quite low. Overall, their weighted mean correlations with specific anxiety diagnoses ranged from only –.09 (panic disorder) to .09 (specific phobia). Thus symptoms of appetite gain do not show strong or consistent associations with any of these mood and anxiety diagnoses.

Summary. Taken together, these analyses yield a very clear pattern. The four symptom dimensions that have the strongest associations with major depression—dysphoria (mean $r = .69$), lassitude (mean $r = .55$), well-being (mean $r = –.50$), and suicidality (mean $r = .49$)—also show the clearest, most compelling evidence of specificity. Put differently, the symptoms that display less impressive specificity—insomnia, appetite loss, and appetite gain—do so, in part, because of their substantially weaker associations with depression (mean *r*s = .36, .35, and .17, respectively). This, in turn, raises the question of whether these weak and nonspecific symptoms actually are necessary, that is, whether they make significant, incremental contributions to the diagnosis of major depression. This is the focus of our next series of analyses.

Incremental Predictive Power

Given that the more specific symptom dimensions had the strongest bivariate associations with major depression, one would expect that they also would emerge as particularly strong contributors in multivariate analyses. To test this expectation, we conducted a series of logistic regression analyses to identify the unique, incremental ability of the individual depression symptoms to predict *DSM-IV* diagnoses of major depression. To facilitate interpretation, the symptom scales were standardized to put them on the same metric.

Table 4.9 presents the odds ratios (ORs) from these analyses. Not surprisingly, dysphoria symptoms—which showed the strongest bivariate association with depression—emerged as a significant predictor in all six analyses, with ORs ranging from 1.83 to 8.59. Only two other types of symptoms made a significant incremental contribution in at least two different analyses: Lassitude symptoms contributed significantly in all three analyses based on interview measures (ORs ranged from 1.73 to 2.60), whereas indicators of well-being yielded significant effects in both of the patient analyses in which they were assessed (ORs = 0.61 and 0.54 in the IDAS and IDAS-CR data, respectively). Overall, these three symptoms dimensions showed incremental predictive power in 11 of 17 analyses (64.7%). Thus three of the symptoms that showed substantial specificity—dysphoria, lassitude, and well-being—also displayed the strongest predictive power in these data.

In contrast, the three symptoms that exhibited little diagnostic specificity—insomnia, appetite loss, and appetite gain—made significant incremental contributions in only 2 of 17 analyses (11.8%). Indeed, insomnia was the only symptom dimension that failed to contribute significantly in any analysis. Overall, therefore, our results indicate that the nonspecific symptoms of depression actually contribute little to its diagnosis.

Implications and Conclusions

In thinking about the implications of these findings, it may be helpful to put them in classic assessment terms. Using this framework as a guide, our data yield

Table 4.9 Odds Ratios from Logistic Regression Analyses Predicting *DSM-IV* Diagnoses of Major Depression

	IDAS			IDAS-CR		
Symptom	Patient	Postpartum	Student	Patient	Student	IMAS
Dysphoria	4.12**	2.08**	8.59**	1.98**	4.66**	1.83**
Lassitude	1.15	1.51	1.09	1.73**	2.60*	2.56**
Suicidality	1.02	1.27	1.19	1.42**	1.65	0.99
Insomnia	1.15	0.92	1.09	1.12	1.12	1.26
Appetite Loss	1.07	1.28	0.81	1.43**	1.10	1.20
Appetite Gain	0.88	0.99	0.70	1.61**	1.14	.—
Well-Being	0.61**	0.77	0.76	0.54**	0.58	.—

Note. N = 894 (IDAS: Patient), 337 (IDAS: Postpartum), 307 (IDAS: Student), 605 (IDAS-CR: Patient), 303 (IDAS-CR: Student), 293 (IMAS). *DSM-IV* = *Diagnostic and Statistical Manual of Mental Disorders* (fourth edition); IDAS = Inventory of Depression and Anxiety Symptoms; IDAS-CR = Clinician Rating version of the IDAS; IMAS = Interview for Mood and Anxiety Symptoms.
* $p < .05$.
** $p < .01$

three basic conclusions. First, symptoms of insomnia and appetite disturbance show relatively poor discriminant validity (i.e., diagnostic specificity) in comparison to indicators of dysphoria, lassitude, suicidality, and well-being. Second, these same symptoms demonstrate unimpressive convergent/criterion validity; that is, they have relatively weak bivariate associations with *DSM-IV* diagnoses of major depression. Third, these symptom dimensions display little or no incremental validity, contributing significantly in only 2 of 17 logistic regression analyses. These final analyses are particularly noteworthy, in that they suggest that these weak, nonspecific symptoms actually may be superfluous in reaching a diagnosis of major depression. This being the case, it seems reasonable to suggest that the diagnosis of depression might be improved by focusing primarily on strong and specific indicators (such as dysphoria, lassitude, and well-being) and deemphasizing relatively weak and nonspecific symptoms, such as insomnia and appetite disturbance.

The findings we have presented here are preliminary, and they clearly need to be replicated and extended in future research. Still, they suggest that it will be useful to scrutinize the properties of these low distress, nonspecific, and poorly functioning symptoms much more closely in the future.

PTSD Symptoms

A Measurement Model for PTSD

DSM-IV groups PTSD symptoms into three clusters: Criterion B (intrusions and reexperiencing of the trauma; five symptoms), Criterion C (emotional numbing and avoidance of trauma-related stimuli; seven symptoms), and Criterion D (manifestations of increased arousal; five symptoms). Although a few studies have supported the three-factor *DSM* scheme, most structural analyses indicate that other models fit the data significantly better (for a meta-analytic review, see Yufik & Simms, 2010). In recent years, the evidence increasingly has converged on two different four-factor structures. The first model, which initially was identified by King, Leskin, King, and Weathers (1998), follows the *DSM-IV* organization, except that the Criterion C symptoms are split into separate Avoidance (two symptoms) and Numbing (five symptoms) factors.

The second model—which was proposed and supported by Simms, Watson, and Doebbeling (2002)—contains Intrusions and Avoidance factors that are identical to those specified in the King et al. (1998) structure. However, its arrangement of the 10 remaining symptoms differs markedly from both the *DSM-IV* and the King et al. (1998) models. Similar to them, it also includes a Hyperarousal factor, but this now is defined by only two of the *DSM-IV* Criterion D symptoms (hypervigilance, exaggerated startle response). The fourth factor in the Simms et al. (2002) structure—Dysphoria—consists of the five Criterion C numbing symptoms (loss of interest, detachment, restricted affect, sense of foreshortened future, inability to recall the trauma) and the three remaining Criterion D

symptoms (sleep disturbance, irritability, difficulty concentrating).

In a recent meta-analytic review of the specificity and correlates of these PTSD symptom dimensions, Gootzeit and Markon (2011) concluded: "Overall, the Simms et al. (2002) model seems better able to separate specific and general variance; whereas dysphoria clearly represents the general factor in this model, the King et al. (1998) model separates this factor into two components: numbing and hyperarousal" (p. 1000). We therefore adopt the Simms et al. (2002) model as our basic measurement framework in the following discussion.

Specificity to PTSD

Relations to depression and anxiety. How specific are these symptoms to PTSD? Although the findings of individual studies have not been entirely consistent (see, e.g., Marshall, Schell, & Miles, 2010), the preponderance of the evidence clearly establishes that indicators of dysphoria display much poorer specificity than other types of PTSD symptoms (see Gootzeit & Markon, 2011; Watson, 2009). For example, in their meta-analytic review, Gootzeit and Markon (2011) examined how the Simms et al. (2002) dimensions correlated with depression and anxiety symptoms (see their Table 4.5). Depression symptoms correlated much more strongly with dysphoria (r = .74) than with hyperarousal (r = .50), intrusions (r = .50), and avoidance (r = .44). The same basic pattern was observed for anxiety symptoms, which also correlated more strongly with dysphoria (r = .58) than with hyperarousal (r = .49), intrusions (r = .40), and avoidance (r = .33).

As was noted by Marshall et al. (2010), simple scale-based analyses potentially suffer from one important confound, namely, that there are many more indicators of dysphoria (eight) than of intrusions (five), avoidance (two), or hyperarousal (two); consequently, dysphoria measures may show stronger correlations with other variables simply because of their greater reliability. Gootzeit and Markon (2011) tested this possibility by creating a composite, nine-item index of Nondysphoria symptoms. Nevertheless, the same basic pattern emerged in these analyses (see their Table 4.8): Depression and anxiety symptoms both correlated more strongly with Dysphoria than with Nondysphoria.

Diagnostic specificity. What about the diagnostic specificity of these symptoms? We examined this issue in a sample of 247 outpatients (for a description of this sample, see Watson et al., 2012). Self-reported PTSD symptoms were assessed using the Civilian Version of the PTSD Checklist (PCL; Weathers, Litz, Herman, Huska, & Keane, 1993), which has 17 items corresponding to the *DSM-IV* symptom criteria for PTSD. As in previous analyses, current *DSM-IV* diagnoses were obtained using the SCID-IV; here, we report results for major depression, PTSD, and panic disorder. The interviewers were graduate students and advanced undergraduate research assistants who all underwent extensive training prior to data collection. Interrater reliability for these diagnoses was examined using 51 audiotaped interviews. The resulting kappas indicated excellent interrater reliability: .92 (major depression), 1.00 (PTSD), and .83 (panic disorder).

Table 4.10 presents polychoric correlations between these *DSM-IV* diagnoses and the PCL; the table displays results both for individual items and for scales based on the Simms et al. (2002) model. It is noteworthy that the intrusions and avoidance symptoms consistently show evidence of good diagnostic specificity, both at the item and the scale level. The five intrusions symptoms had correlations with PTSD ranging from .60 to .65, with a mean value of .63; in contrast, their average correlations with major depression and panic disorder were only .27 and .45, respectively; similarly, the two avoidance symptoms had mean correlations of .60 (PTSD), .36 (major depression), and .42 (panic disorder).

The hyperarousal and dysphoria symptoms generally show much poorer specificity. The hyperarousal symptoms had virtually identical correlations with PTSD and panic disorder, both at the item and the scale level. These data are consistent with previous evidence establishing that indicators of anxious arousal are substantially related to both panic disorder and PTSD (Brown et al., 1998; Watson, 2009).

The findings for the dysphoria symptoms are more complex. Five of the items (loss of interest in activities, feeling distant or cut off, feeling emotionally numb, irritability, difficulty concentrating) actually show specificity to depression rather than to PTSD: That is, they correlate much more strongly with diagnoses of major depression (mean r = .58) than with either PTSD (mean r = .36) or panic disorder (r = .28). In contrast, the item measuring Criterion C3 (memory problems) showed some specificity to panic disorder. Finally, the two remaining symptoms (feeling the future will be cut short, trouble falling or staying asleep) displayed relatively weak and nonspecific associations with all three disorders (rs ranged from .30 to .39). In this regard, it is noteworthy that we again see evidence

Table 4.10 Polychoric Correlations Between the PCL Scales and Items and *DSM-IV* Diagnoses

Paraphrased PCL Item	MDD	PTSD	Panic
Intrusions	.29	***.71***	***.48***
Repeated, disturbing memories	.29	***.65***	.42
Repeated, disturbing dreams	.25	***.62***	.44
Reliving a stressful experience	.25	***.60***	.41
Feeling upset when reminded of event	.29	***.65***	***.45***
Had physical reaction when reminded	.26	***.61***	***.55***
Avoidance	.37	***.63***	***.45***
Avoided thinking/talking about event	.35	***.62***	.39
Avoided activities/situations	.37	***.57***	***.45***
Dysphoria	***.68***	***.50***	.39
Trouble remembering parts of event	.10	.29	.39
Loss of interest in activities	***.69***	.39	.34
Feeling distant or cut off	***.66***	***.46***	.29
Feeling emotionally numb	***.57***	.40	.28
Feeling future will be cut short	.39	.37	.30
Trouble falling or staying asleep	.36	.34	.33
Feeling irritable/angry outbursts	.42	.25	.17
Difficulty concentrating	***.56***	.31	.30
Hyperarousal	.34	***.51***	***.49***
Being "superalert," watchful	.24	***.48***	***.47***
Feeling jumpy, easily startled	.39	***.46***	***.47***

Note. $N = 247$. Correlations ≥ |.45| are highlighted. PCL = PTSD Checklist; *DSM-IV* = *Diagnostic and Statistical Manual of Mental Disorders* (fourth edition); MDD = major depression; PTSD = posttraumatic stress disorder. These results are based on Patient Sample 4 from Watson et al. (2012).

that indicators of insomnia (as assessed here by an item tapping PTSD Criterion D1) show relatively weak and nonspecific associations with *DSM-IV* mood and anxiety disorders.

Incremental Predictive Power

We examined the incremental predictive power of individual PTSD symptoms by conducting a logistic regression analysis in which the four Simms et al. (2002) factor scales were used to predict PTSD diagnoses; again, scale scores were standardized to put them on the same metric. Only Intrusions (OR = 2.82, $p < .01$) showed significant incremental power in these analyses; Avoidance (OR = 1.19), Dysphoria (OR = 1.19), and Hyperarousal (OR = 1.25) all failed to contribute significantly to the prediction of PTSD diagnoses.

Implications and Conclusions

PTSD symptoms show the same general pattern observed earlier in our examination of depression. Most notably, it now is clear that these symptoms vary widely in their specificity. In particular, extensive evidence establishes that indicators of dysphoria display much poorer specificity than other types of PTSD symptoms: They correlated more strongly with depression and anxiety symptoms (Gootzeit & Markon, 2011; Watson, 2009) and failed to show any diagnostic specificity to PTSD in our outpatient sample (and, in fact, actually had a stronger association with major depression). Hyperarousal symptoms also failed to demonstrate diagnostic specificity in our data, correlating equally with panic disorder. In contrast, indicators of intrusions and avoidance exhibited stronger and more consistent evidence of specificity. Finally, our outpatient analyses indicated that these nonspecific dysphoria and hyperarousal symptoms had somewhat weaker bivariate correlations with *DSM-IV* diagnoses of PTSD and failed to provide significant incremental information in a logistic regression analysis. Although these incremental validity analyses were based on a single sample, they tentatively suggest that these nonspecific symptoms may not provide information that is essential in reaching a diagnosis of PTSD.

In light of these findings, it seems reasonable to suggest that the diagnosis of PTSD might be improved by focusing primarily on strong and specific indicators (i.e., intrusions and avoidance) and deemphasizing relatively weak and nonspecific symptoms (i.e., dysphoria and hyperarousal). The situation here is complicated, however, by two additional considerations. First, in their meta-analytic examination, Gootzeit and Markon (2011) reported that trauma history correlated more strongly with dysphoria symptoms ($r = .35$) than with intrusions ($r = .28$), hyperarousal ($r = .20$), and avoidance ($r = .19$). Gootzeit and Markon (2011) concluded that these findings suggest that "dysphoria symptoms are an important part of the overall construct

of PTSD, and likely provide important clinical information" (p. 1000).

Second, in an analysis of the National Comorbidity Survey Replication data, Elhai, Grubaugh, Kashdan, and Frueh (2008) examined an alternative set of diagnostic criteria (developed by Spitzer, First, and Wakefield, 2007) that eliminates the five PTSD symptoms that directly overlap with other internalizing disorders (C3: amnesia, C4: loss of interest, D1: sleep disturbance, D2: irritability, D3: difficulty concentrating). These modifications eliminated five of the eight indicators of the Simms et al. (2002) Dysphoria factor. Consequently, one would expect that these revised diagnostic criteria would contain a somewhat weaker general distress component and show greater diagnostic specificity to PTSD. Nevertheless, Elhai et al. (2008) found that the rates of comorbidity between PTSD and other disorders essentially remained unchanged regardless of the diagnostic criteria that were used. Grubaugh, Long, Elhai, Frueh, and Magruder (2010) subsequently replicated these results in a sample of veterans. These findings have been interpreted as demonstrating that deemphasizing—or even removing—nonspecific PTSD symptoms actually would have little effect on key diagnostic problems such as comorbidity (Elhai et al., 2008; Grubaugh et al., 2010; see also Gootzeit & Markon, 2011).

Alternatively, however, these results simply may show that it is insufficient to eliminate only a subset of the dysphoria symptoms. Indeed, Table 4.10 indicates that two of the retained dysphoria symptoms (C5: feeling distant or cut off, C6: feeling emotionally numb) are strongly related to depression (*r*s = .66 and .59, respectively). Thus it remains possible that eliminating all eight markers of dysphoria will enhance the diagnosis of PTSD in a significant way. We tested this idea by creating four different versions of the PCL. The first version (PCL-17) includes all 17 items, thereby modeling the *DSM-IV* diagnosis of PTSD. The second version (PCL-12) drops the five symptoms that directly overlap with other internalizing disorders; it therefore captures the reduced model proposed by Spitzer et al. (2007) and investigated subsequently by Elhai et al. (2008) and Grubaugh et al. (2010). The third version (PCL-9) removes all eight dysphoria items, thereby modeling the effects of eliminating this entire factor from the disorder. The final version (PCL-7) further eliminates the two hyperarousal items; it therefore estimates the effects of restricting diagnosis and assessment to the two most specific symptom clusters (intrusions and avoidance).

Table 4.11 presents polychoric correlations between these four PCL variants and diagnoses of major depression, PTSD, and panic disorder in our sample of 247 outpatients. Consistent with the results of Elhai et al. (2008) and Grubaugh et al., (2010), our data indicate that dropping the five overlapping dysphoria symptoms has surprisingly little effect: Correlations with PTSD (.69 vs .70) and panic disorder (.50 vs..51) essentially remain unchanged, whereas the association with major depression declines only modestly (from .56 to .47). In contrast, eliminating additional symptoms appears to offer more substantial benefits. Eliminating the entire dysphoria cluster (PCL-9) substantially reduces the correlation with major depression (r = .34) but does not affect the overlap with panic disorder (r = .52). Overall, PCL-7 (i.e., focusing exclusively on the intrusions and avoidance symptoms) displays the best convergent/discriminant pattern in these data: It has the weakest associations with both major depression (r = .30) and panic disorder (r = .49) while maintaining a very strong correlation with PTSD diagnoses (r = .71).

In light of these data, we continue to believe that the diagnosis and assessment of PTSD potentially can be improved by focusing primarily on more specific types of symptoms. This issue merits careful attention in future research.

Future Research Directions

The results we have presented here need to be replicated and extended in several ways. First, our analyses were limited to unipolar mood and anxiety disorder diagnoses. However, the problem of comorbidity is not limited to the mood and anxiety disorders but rather pervades the entire *DSM* (Mineka et al., 1998; Widiger & Clark, 2000). It therefore

Table 4.11 Polychoric Correlations Between Alternative Versions of the PCL and *DSM-IV* Diagnoses

PCL Version	MDD	PTSD	Panic
PCL-17	***.56***	***.69***	***.50***
PCL-12	***.47***	***.70***	***.51***
PCL-9	.34	***.71***	***.52***
PCL-7	.30	***.71***	***.49***

Note. N = 247. Correlations ≥ |.45| are highlighted. See text for details. PCL = PTSD Checklist; *DSM-IV* = *Diagnostic and Statistical Manual of Mental Disorders* (fourth edition); MDD = major depression; PTSD = posttraumatic stress disorder. These results are based on Patient Sample 4 from Watson et al. (2012).

will be important to examine a broader array of symptoms and a wider range of disorders in future research. For example, as discussed earlier, Carney et al. (2009) noted that many depression symptoms are also essential features of primary insomnia (e.g., insomnia, mood disturbance, fatigue/anergia, impaired concentration). Consequently, it is possible that some depression symptoms that show good specificity vis-à-vis anxiety—such as dysphoria and lassitude—may exhibit more limited specificity when examined in relation to sleep disorders. Conversely, symptoms of appetite gain—which displayed consistently weak associations with disorders in our analyses—appears to show stronger, more specific associations with seasonal forms of depression (e.g., Wehr et al., 1991). More generally, broader, more comprehensive approaches to assessment can be highly informative in explicating the basic properties of symptoms and in identifying shared features that give rise to comorbidity.

Second, although we examined how both self-reported and clinician-rated symptoms were related to various disorders, our diagnostic data were derived from a semi-structured interview (the SCID-IV) that employed skip-outs; because of this, we lacked complete symptom-level interview data and, therefore, were not able to model the direct effects of removing different types of symptoms from the target diagnoses. As noted previously, the work of Elhai et al. (2008) and Grubaugh et al. (2010) highlights the importance of modeling these symptom-based effects directly. For example, Grubaugh et al. (2010) used the Clinician-Administered PTSD Scale (Blake et al., 1995)—a 30-item structured interview that corresponds to the *DSM-IV* criteria for PTSD—to derive PTSD diagnoses. Because the Clinician-Administered PTSD Scale does not involve skip-outs, Grubaugh et al. (2010) were able to compare comorbidity rates for (a) standard PTSD diagnoses versus (b) the reduced symptom criteria proposed by Spitzer et al. (2007). As discussed earlier, they found that the rates of comorbidity between PTSD and other disorders essentially remained unchanged regardless of the symptom criteria that were used. Our own data (see Table 4.11) strongly suggest that a more radical pruning of the symptom criteria may be effective in substantially lowering the comorbidity between PTSD and depression; obviously, however, it is necessary to test the effects of removing these symptoms directly before any clear conclusions can be drawn.

Finally, another key limitation of the current analyses is that our data are completely cross-sectional in nature. Long-term longitudinal studies are needed to examine how the associations between symptoms and diagnoses change over time. To take one example, dissociative symptoms appear to play a particularly important role in acute reactions to trauma and may be a risk factor for the subsequent development of PTSD (for a discussion of this issue, see Cardeña & Carlson, 2011). More generally, it seems likely that many symptom-disorder relations are dynamic and change significantly across acute versus chronic phases of disorders.

Clinical Implications

Although our findings warrant further research and replication, they potentially have important implications for direct clinical intervention, particularly with regard to assessment and diagnosis. Our first major finding—that certain symptoms do not demonstrate specificity to their disorder—has clear consequences for differential diagnosis. For instance, symptoms of insomnia and eating disturbance relate equally to measures of depression and anxiety; thus, assessing these symptoms when working with a new client who may have major depression would not facilitate the clinician's ability to make a diagnosis, which is typically the goal in an initial assessment. Removing those symptoms that lack specificity and demonstrate diagnostic overlap from the initial diagnostic assessment may significantly enhance the assessor's ability to make a differential diagnosis.

Our second finding—that some symptoms lack the power to predict their associated *DSM-IV* diagnosis—also has important implications for diagnostic efficiency. For instance, based on our data, it appears that assessing dysphoria and hyperarousal symptoms does not provide any incremental information relevant to the diagnosis of PTSD, once intrusions and avoidance have been considered. Removing symptoms that do not add to the diagnosis can streamline the assessment process and facilitate the generation of a more efficient—and equally accurate—diagnosis. In a busy practice, time-effective assessment is vital.

Of course, symptoms of insomnia, appetite disturbance, and hyperarousal are distressing and may be clinically important in their own right; they therefore are appropriate targets in the treatment of clients with major depression or PTSD, just as they would be in the many other disorders in which they are an obvious symptom. We are not suggesting

that these types of symptoms are unimportant or clinically uninteresting; rather, we are arguing that their assessment is not a necessary part of the initial assessment and their removal as diagnostic criteria may, in fact, enhance efficient differential diagnosis.

Conclusion

Disorders such as major depression and PTSD represent heterogeneous combinations of distinct types of symptoms. We believe that analyses focusing on these distinctive symptom dimensions can play an important role in explicating key diagnostic phenomena such as comorbidity. In this chapter, we have examined symptom dimensions within depression and PTSD from the perspective of the quadripartite model, which posits that it is important to consider two quantitative elements when analyzing the properties of symptoms: (a) the magnitude of their general distress component and (b) their level of specificity.

Our review highlighted the heuristic value of this framework. With regard to depression, the evidence establishes that some symptoms containing a strong general distress component (e.g., dysphoria, lassitude) nevertheless show substantial evidence of specificity. In contrast, symptoms of insomnia and appetite disturbance—which are less saturated with general distress variance—demonstrate little or no specificity. Moreover, these same symptoms have relatively weak bivariate associations with *DSM-IV* diagnoses of major depression and displayed little or no incremental validity in logistic regression analyses. In the case of PTSD, our analyses indicated that it was the symptoms with the strongest general distress component (i.e., indicators of the Simms et al. [2002] Dysphoria factor) that showed poor specificity, relatively weak bivariate associations with the diagnosis, and no incremental validity in logistic regression analyses.

Within both disorders, we identified symptoms that both (a) exhibited poor diagnostic specificity and (b) provided little or no incremental information to their respective diagnoses. Put differently, our results indicate that the nonspecific symptoms of these disorders actually contribute very little to their diagnosis. This being the case, we have suggested that the diagnosis and assessment of these disorders potentially can be improved by focusing primarily on more specific types of symptoms. The available evidence regarding such key issues as diagnostic specificity and incremental validity remains rather limited, however, so it clearly will be important to examine them further in the future. We hope that the theoretical considerations and empirical data we have reviewed in this chapter will stimulate further research into these issues and, more generally, into the nature and properties of distinctive types of symptoms.

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CHAPTER

5 Depressive Disorders, Comorbidity Issues, and Assessment Strategies

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Abstract

Assessment is at the very core of clinical and research endeavors to understand and ameliorate depressive disorders. In the current chapter, we discuss pressing issues in assessment of depressive disorders beginning with the definitional: how these disorders are conceptualized and classified. We highlight the *DSM-IV-TR* nosological organization of depressive disorders, and those disorders that are closely related (e.g., anxiety and adjustment disorders), as well as current depressive disorder proposals for the upcoming *DSM-5*. The high rates of comorbidity among the depressive and related disorders are discussed as an assessment challenge, and we propose a unified latent structure framework to supplement clinical assessment that involves characterizing individuals' levels of underlying internalizing disorder liability. We discuss how disorders, and the latent internalizing liability, may manifest differently across subpopulations, such as age and ethnicity/culture. Finally, we discuss psychometric issues and conclude with a list of critical unanswered questions in depressive disorder assessment.

Key Words: assessment, depressive disorders, depression, comorbidity, internalizing, neuroticism

Assessment of psychopathology is at the very foundation of mental health efforts. Psychologists, psychiatrists, counselors, social workers, and other health-care workers utilize clinical assessment to investigate the signs and symptoms of patients and to develop treatment plans toward symptom amelioration. Similarly, the basis of science is measurement. As such, researchers use assessment procedures to characterize the psychopathology of their participants, drawing inferences and testing hypotheses about the nature of mental disorder. Managed-care entities determine reimbursement schedules in large part by diagnosis, and assessment is at the core of these diagnoses. Assessment is, thus, a critical component of all endeavors relating to the classification, understanding, and treatment of psychopathology.

Assessment in general is a broad topic with myriad considerations, although the ultimate goal is to capture the phenomena of interest adequately. No single assessment instrument or process will be adequate for all purposes, however, complicating matters further. For instance, if one's purpose is to identify individuals, at the population level, experiencing depressive symptomatology in hopes of improving public health (e.g., for National Depression Screening Day; Baer et al., 2000), a brief screening measure would likely be adequate as well as necessary. If one's purpose to create four highly homogeneous groups of individuals with (1) major depression, (2) dysthymia, (3) a nondepressive mental disorder, and (4) no psychopathology (i.e., healthy controls) to test the efficacy of a new antidepressant medication, lengthy and in-depth assessment facilitating this complex differential diagnosis will likely be required. Other considerations in evaluating assessment measures include measures' psychometric properties of reliability and validity,

expense, information source (e.g., clinician-, self-, or informant-report), time requirements, and so on. These factors may change in different contexts (e.g., psychometric properties being different across populations; time to complete assessment may differ between depressed individuals in a university mental-health center versus a traumatic brain injury clinic).

Even by restricting our discussion to assessment of depressive disorders, we are still left with a topic far too broad to cover fully in any single chapter or book. Our purpose in the current chapter is to highlight several of the most salient and pressing issues in the assessment of depressive disorders. These include classification issues and nosology, comorbidity among the disorders, and general diversity considerations, including how assessment measures—and perhaps the depressive-disorder constructs themselves—differ nontrivially across populations. We will not provide a full review of specific measures of depressive disorders, given that over 280 such measures have been developed (Santor, Gregus, & Welch, 2006). Several excellent resources review the characteristics of the most widely used depressive disorder assessment instruments, and interested readers are referred to those works for additional information (see Nezu, Nezu, Friedman, & Lee, 2009; Nezu, Ronan, Meadows, & McClure, 2000). We begin with a discussion of definitional issues in depressive disorders.

Classification Issues in Depressive Disorders

Classification of latent constructs

Clinical assessment is primarily intended to determine the presence (versus absence) of psychopathology, and, if present, to measure its degree of severity. Thus, mental disorder constructs are the focus of, and foundation for, clinical assessment. As in many other scientific disciplines, measurement in the allied mental-health fields is complicated by the very constructs we wish to assess, because they are *latent*. That is, "psychopathology," as it exists in nature, is unobservable directly. We must, thus, operationalize it as the conjunction of multiple manifest (directly observable) indicators. Such conjunctions are known as latent variables because they are inferred from multiple direct observations. For example, major depression is not just insomnia, because insomnia (although directly observable) must occur in the context of additional observable indicators (e.g., self-reported low mood) to infer the existence of an episode of depression.

Let us consider an example from another discipline, nutrition, to illustrate why the assessment of psychopathology is complicated by its very definition. If a nutritionist is interested in measuring, say, the weight of a patient, she is presented with a single physical entity, the patient (who weighs a particular amount). The nutritionist has a clear definition of the construct he or she wants to assess, weight. The nutritionist also has a standard metric to characterize the patient's weight in kilograms (or pounds). Finally, the nutritionist has a highly reliable assessment instrument, a scale.

Now, consider a clinical psychologist who is asked to assess whether a given patient, who appears sad, is depressed and, if so, what level of severity the depression reaches. Depression, unlike weight, is a construct that is not directly observable. Through years of experience gained by mental-health workers, there has been a broad consensus that there exists, in some patients, a phenomenon associated with low mood, disinterest in activities, disturbances in thinking and concentration, and other symptoms. When these signs and symptoms occur together in particular patterns and for a given duration, clinicians have agreed to conceptualize this constellation of pathology as a major depressive episode. Thus, the phenomenon in question is not directly observable as weight is. It is the result of clinical experience and consensus—a latent construct that cannot be measured directly.

There is no equivalent of the nutritionist's scale for depression; there is no gold-standard ruler or yardstick. Instead, clinicians have attempted to define the signs and symptoms that appear most closely related to depression, which form the diagnostic criteria for major depression in official classification systems, such as the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*). Beginning largely with *DSM-III* (American Psychiatric Association, 1980), there was an attempt to define discrete signs and symptoms of mental disorders that could be assessed reliably, with the aim of yielding reliable diagnoses. This is in stark contrast to other possible approaches, such as one requiring untestable, and likely unreliable, psychodynamic clinical inferences about, for instance, the origins of the mood disturbance. The current version of the diagnostic manual, *DSM-IV-TR* (American Psychiatric Association, 2000), lists nine diagnostic criteria for a major depressive episode and requires at least five of these to be present during the same two-week period, and represent a change from previous functioning, for a major depressive episode to

be deemed present. It is the purpose of diagnostic clinical assessment of the major depression diagnosis to ascertain if a patient's symptomatology fits the definition given in *DSM*. However, we now see that the definition itself reflects assessment considerations, and, in this way, assessment has informed classification on a fundamental level. Alternatively, classification delineates the focus of clinical assessment. As such, we will first turn our attention to classification issues of the depressive and related disorders.

DSM-IV-TR depressive disorders

The *DSM-IV-TR* divides mental disorders first into Axes, with Axis I disorders representing what are sometimes referred to as "clinical disorders" and with Axis II representing personality disorders and mental retardation. Within Axis I, disorders are organized into conceptually similar groups, such as anxiety disorders, eating disorders, and sleep disorders. "Mood disorders" represents another group of disorders, and *DSM-IV-TR* divides this category into depressive disorders and bipolar disorders. The primary depressive disorders listed are major depressive disorder, dysthymic disorder, and depressive disorder NOS (not otherwise specified). To illustrate clinical assessment using the *DSM-IV-TR*, we will now characterize the process by which one can receive a diagnosis of major depressive disorder.

The foundation of assessment for depression in *DSM-IV-TR* is the *major depressive episode*. Assessment involves characterizing whether at least five of nine diagnostic criteria have been present during the same two-week period and represent a change from previous functioning. First, either (1) depressed mood or (2) anhedonia (i.e., diminished interest or pleasure in activities) must be present. Other criteria include (3) weight loss or gain, or increase or decrease in appetite, (4) insomnia or hypersomnia, (5) psychomotor agitation or retardation, (6) fatigue or loss of energy, (7) feelings of worthlessness or guilt, (8) diminished ability to think or concentrate, or indecisiveness, and (9) recurrent thoughts of death, suicidal ideation, suicide planning, or a suicide attempt. The present symptoms must cause significant distress or impairment, must not be due to the direct physiological effects of a substance or general medication condition, and must not meet criteria for a mixed episode (i.e., simultaneous manic and major depressive episodes). Finally, if the individual has lost a loved one recently, the symptoms must last longer than two months after the death or be associated with notable impairment, preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation. This latter consideration is known as the bereavement exclusion, which putatively distinguishes between "normal grief" and a major depressive episode.

As we can see, the assessment of a major depressive episode is quite a complex undertaking if done in full compliance with the *DSM-IV-TR* system. The major depressive episode, however, is not considered a mental disorder, and it cannot be used as a diagnosis; rather, it forms the foundation for a diagnosis of *major depressive disorder*. Major depressive disorder requires (1) the presence of a major depressive episode, (2) no history of a manic, mixed, or hypomanic episode, and (3) the major depressive episode is not better accounted for, or superimposed on, other disorders (i.e., schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder, or psychotic disorder NOS). If one such episode has occurred, the modifier "single episode" is used; if more than one major depressive episode has occurred, the modifier "recurrent" is used. Thus, the diagnosis of major depressive disorder technically requires (1) assessment of the possible presence of a major depressive episode currently, (2) assessment of possible previous major depressive episodes, (3) assessment of previous manic, mixed, and hypomanic episodes, and (4) assessment of the rule-out disorders.

After making a diagnosis of major depressive disorder, a variety of specifiers are included in *DSM-IV-TR* to characterize the disorder further. First, clinicians must specify the severity of the major depressive episode, with severity options of mild, moderate, severe without psychotic features, and severe with psychotic features. If psychotic features are present, they can be specified as mood-congruent or mood-incongruent. Other possible features to be assessed are catatonic, melancholic, and atypical features. If the major depressive episode has been continually present for at least two years, a specifier of *chronic* can be applied. Longitudinal course of major depressive disorder can be specified as being *with or without full interepisode recovery*. If onset of the major depressive episode occurred within four weeks of giving birth, a specifier of *with postpartum onset* can be applied. A *seasonal pattern* specifier can be given when the mood disturbance fluctuates in tandem with times of the year. Finally, if the full criteria for a major depressive episode are not met currently, the major depressive disorder can be specified as being *in partial* or *in full remission*.

The *DSM-IV-TR* also lists dysthymic disorder and depressive disorder NOS as depressive disorders. *Dysthymic disorder* is long-term depressed mood, with some associated additional symptoms, that is not better conceptualized as chronic major depressive disorder, major depressive disorder in partial remission, or as a bipolar mood disorder. Unlike major depressive disorder, which requires the presence of a major depressive episode for diagnosis, dysthymic disorder is considered present when at least two years of depressive symptomatology have occurred. During the first two years of the mood disturbance, no major depressive episodes may have occurred; major depressive episodes may have occurred prior to this two-year period, providing they were in full remission before onset of dysthymia.

As can be seen, the construct of dysthymic disorder is related quite strongly to major depressive episodes/disorder. Indeed, there is significant overlap not only in the general focus on depressed mood but also in the associated symptoms. Dysthymia requires the presence of two or more of the following: (1) poor appetite or overeating, (2) insomnia or hypersomnia, (3) low energy or fatigue, (4) low self-esteem, (5) poor concentration or difficulty making decisions, and (6) feelings of hopelessness. With the exception of low self-esteem, these diagnostic criteria overlap directly with those of a major depressive episode.

Assessment, for the purpose of differential diagnosis, between major depressive episodes/disorder and dysthymia relies on careful characterization of the length of the mood disturbance and the breadth of the symptoms that are present. This requires retrospection on the part of the patient, which can be fallible (Moffitt et al., 2010). Clinicians may also seek collateral information, such as informant-report information or medical records. Finally, although *DSM-IV-TR* states that there must be a two-year period of dysthymia free of major depressive episodes at its onset, it leaves open the possibility of later diagnostic comorbidity. That is, after dysthymia has been established, it is possible that patients will experience an increase in symptoms, resulting in a simultaneous major depressive episode. This comorbidity pattern, sometimes referred to as "double depression," represents a major depressive episode superimposed upon long-standing dysthymic disorder.

Depressive disorder NOS is a broad and potentially heterogeneous diagnostic construct. It is diagnosed when depressive features are present but diagnostic criteria are not met for any particular disorder. *DSM-IV-TR* lists a variety of possibilities for depressive disorder NOS, including premenstrual dysphoric disorder—a marked change in depressive and related symptoms during most menstrual cycles. Other possibilities include depressive symptoms that do not meet severity or duration criteria for a major depressive episode or dysthymic disorder.

The NOS diagnoses of *DSM-IV-TR* present a challenge for assessment. Their inclusion in the diagnostic system allows for mental-health-care workers to provide a diagnosis (and bill for services) when the specific disorders in the nosology fail to characterize adequately the experience of the patient. In this way, NOS diagnoses require ruling out the presence of multiple other possible disorders, which is a time-consuming and complex process. Unfortunately, given limited resources and other constraints frequently placed upon clinical practice, NOS diagnoses are often improperly used to characterize symptoms when a full assessment is not completed. In other words, from an assessment perspective, a diagnosis of depressive disorder NOS may reflect a bona fide diagnosis of depressive psychopathology or an inability/unwillingness on the part of the provider to engage in careful and detailed assessment. The research literature suggests that NOS disorders are among the most commonly applied diagnoses within groups of disorders (e.g., Clark, Livesley, & Morey, 1997; Fairburn & Bohn, 2005; Lenzenweger, Loranger, Korfine, & Neff, 1997; Pagan, Oltmanns, Whitmore, & Turkheimer, 2005). There is likely a genuine need for NOS disorders within the current classification system, but their clinical utility is greatly depleted when their diagnosis represents lackadaisical assessment rather than a "best fit" diagnosis.

DSM-IV-TR depressive-related disorders

As we have seen, the current classification system conceptualizes depressive disorders into major depressive disorder, dysthymic disorder, and depressive disorder NOS. In terms of clinical assessment and differential diagnosis, these disorders differ largely in symptom breadth (i.e., how many diagnostic criteria are present) and duration. Other, nondepressive *DSM-IV-TR* disorders, however, can be associated with mood disturbance and can present with depressive features. We will briefly discuss a few of these disorders, because clinical assessment and differential diagnosis frequently require their consideration, either as diagnoses to rule out or as diagnoses that account for observed depressivity.

One diagnosis closely related to the "official" depressive disorders is *depressive personality disorder*, which is included in the appendix of *DSM-IV-TR* as a criterion set for further study. The essential feature of depressive personality disorder is "a pervasive pattern of depressive cognitions and behaviors that begins by early adulthood and that occurs in a variety of contexts" (p. 788). Personality disorders such as depressive personality disorder are conceptualized as enduring forms of psychopathology that manifest across multiple constructs and are lengthy (e.g., lifelong) in duration. Given these duration considerations, there is clear overlap between dysthymic disorder and depressive personality disorder—both are long-term phenomena with a core of depressivity. In terms of differential diagnosis, depressive personality disorder's diagnostic criteria focus more on cognitive, interpersonal, and intrapsychic personality traits than do those of dysthymic disorder. For instance, the diagnostic criteria of depressive personality disorder include feeling pessimistic (cognitive), being judgmental and critical toward others (interpersonal), and having a critical, blaming, and derogatory attitude toward the self (intrapsychic). Further, the onset of depressive personality disorder should have occurred by early adulthood, which is not necessarily the case for dysthymia. These rather fine-grained distinctions require very careful clinical assessment of onset, duration, pervasiveness, and precise nature of the depressive symptoms the patient is experiencing. The importance of the distinction between these two disorders, however, is probably one of clinical judgment; this is highlighted by the inclusion of depressive personality disorder in a supplementary appendix rather than the main body text, and given that depressive personality disorder is diagnosed formally as personality disorder NOS. Indeed, *DSM-IV-TR* notes that it "remains controversial whether the distinction between depressive personality disorder and Dysthymic Disorder is useful" (p. 788).

Within the mood disorders section of *DSM-IV-TR* are the bipolar disorders, which relate closely to the depressive disorders in many ways. These disorders, broadly, comprise *bipolar I disorder*, *bipolar II disorder*, *cyclothymic disorder*, and *bipolar disorder NOS*. The disorders all require the presence of at least one hypomanic, manic, or mixed episode. In terms of assessment of depressive disorders, it is critical to determine any history of these episodes, because, if such an episode has been present in the patient's life, a diagnosis of major depressive disorder or dysthymia must be ruled out. These latter, depressive diagnoses are considered "unipolar" disorders—that is, they are associated with only a single pole of a mood dimension, the low pole. This is in contrast to bipolar disorders, which are most typically associated with the elevated and low poles of mood. Finally, the mood disorders section also includes "other mood disorders," including *mood disorder due to a general medical condition*, *substance-induced mood disorder*, and *mood disorder NOS*.

Although bipolar I disorder can technically occur without a history of a major depressive episode, bipolar II disorder requires the presence or history of a major depressive episode. The overlap here with major depressive disorder is clear, given that both disorders require a major depressive episode. The differential diagnosis between bipolar II disorder and the depressive disorders requires assessment for the presence, or positive history, of a hypomanic episode. If hypomania has ever been present, a diagnosis of bipolar II disorder is appropriate rather than a diagnosis of major depressive disorder. Clinically, though, assessment for hypomania (or mania) is complicated by the possibility of dysphoric hypomania. Rather than the elevated, expansive mood often considered a hallmark of (hypo)mania, *DSM-IV-TR* allows for (hypo)manic episodes instead to be associated with irritable mood. Because the diagnostic criteria for a hypomanic episode include several signs and symptoms that could be interpreted as representative of a major depressive episode (e.g., decreased need for sleep, distractibility, psychomotor agitation), careful assessment to characterize the precise nature of the episode is necessary.

Althougj depressive personality disorder and the bipolar disorders present perhaps the most complicated issues in the assessment of depressive disorders, other *DSM-IV-TR* disorders and phenomena can show substantial overlap as well. We will not belabor this point, but it is important to touch briefly on three such constructs. First, *anxiety disorders* are commonly comorbid with depressive disorders (Krueger & Markon, 2006; Watson, 2005, 2009), and some anxiety disorders share features with some depressive disorders. For instance, *generalized anxiety disorder* has diagnostic criteria involving psychomotor agitation, fatigue, difficulty concentrating, irritability, and sleep disturbance. Differential diagnosis between generalized anxiety disorder and the depressive disorder requires assessment of whether the symptoms arise from worry and anxiety or are associated with low mood disturbance, respectively.

Adjustment disorder results from exposure to one or more identifiable stressors that lead to emotional or behavioral symptoms; adjustment disorder with depressed mood is a subtype defined predominantly by depressed mood, feelings of hopelessness, and tearfulness, and, thus, can present similarly to depressive disorders. Clinical assessment should focus on the identification of a stressor and how closely the symptoms relate to postexposure adjustment. Finally, *bereavement* after the death of a loved one, listed among "other conditions that may be a focus of clinical attention" and thus not diagnostic, can closely mirror the symptoms of a major depressive episode. Major depressive disorder is usually not diagnosed for at least two months after the loss, unless atypical grief reactions (e.g., hallucinatory experiences, morbid preoccupation with worthlessness) occur.

Physical problems overlapping with depressive disorders

As we noted earlier, mood disorder due to a general medical condition is listed in the *DSM-IV-TR* to capture depressive symptoms (or other mood symptoms) resulting from physical problems. For instance, metabolic issues may lead to onset of mood pathology. Other somatic issues, however, may produce symptoms that closely mirror those of the depressive disorders but are not bona fide depressive disorders. For instance, individuals with obesity may report symptoms such as fatigue, hypersomnia, psychomotor retardation, appetite changes, and feelings of worthlessness or inappropriate guilt. Individuals with obstructive sleep apnea may show daytime fatigue, fragmented sleep, psychomotor retardation, and reduced ability to think or concentrate due to daytime fatigue. The crucial assessment considerations here involve the presence or absence of low mood and/or anhedonia.

DSM-5 depressive disorders

The diagnostic classification system is currently undergoing revision toward the next edition: *DSM-5*. (The DSM-5 was released on May 22, 2013. However, this chapter was completed before the release date.) The *DSM-5* Task Force and various Work Groups are now in the process of drafting this next version of the official nosology, which is slated for publication in 2013. (The other primary nosology, the *International Classification of Diseases* [*ICD*] is simultaneously undergoing revision as well.) As such, any discussion of what the future holds for diagnostic classification, and, thus, assessment, of depressive and related disorders is tentative at best at this point. We will discuss briefly the most recent developments in depressive disorder classification toward *DSM-5*, based on distributed reports from the *DSM-5* Mood Disorders Work Group. This information is available at http://www.dsm5.org for interested readers who want the most current information about the revision.

The current *DSM-5* depressive-disorders proposal has expanded the depressive disorders notably. *Major depressive disorder* (single episode and recurrent) and *chronic depressive disorder* (dysthymia) remain as diagnoses. Also included are *substance-induced depressive disorder*, *depressive disorder associated with a known general medical condition*, and *depressive conditions not elsewhere classified*, which have clear overlap with some *DSM-IV-TR* mood disorder constructs. *Disruptive mood dysregulation disorder* is a proposed diagnosis involving temper outbursts occurring on otherwise negative mood. *Premenstrual dysphoric disorder* concerns mood changes (e.g., depressed mood, mood swings, irritability) that are temporally linked with the menstrual cycle. *Mixed anxiety/depression* is defined as meeting three or four diagnostic criteria for a major depression and also experiencing anxious distress (e.g., irrational worry, motor tension, preoccupation with unpleasant worries).

Because these revisions are currently tentative, it is not profitable to discuss them at length in the current report. Some of these changes are substantial though, and they have evoked notable controversy. Among the most controversial proposed changes to the depressive disorders has been the removal of the bereavement exclusion when assessing for a major depressive episode. This removal was justified by empirical evidence that loss of a loved one does not differ significantly from the myriad other stressors that can precipitate a major depressive episode (Zisook & Kendler, 2007). The controversy around this change revolves around several issues. For one, it is possible that this removal could pathologize "normal" grief reactions after the death of a loved one, classifying a typical and expected human experience as a mental disorder. Another concern is that such a change could lead to increased diagnosis of major depressive disorder, thus inflating the prevalence rates. This would give the appearance to some that major depressive disorder is occurring with greater frequency, although it would actually represent expanding the purview of the major depressive disorder diagnosis such that it would include more cases.

Classification implications for assessment

To summarize, the *DSM*s—editions past, current, and apparently future—have classified depressive psychopathology broadly by parsing it into a variety of smaller units. This classification has moved over the years to focus on diagnostic criteria, rather than narrative paragraphs, that can be assessed individually. Ideally, diagnostic criteria should be assessable in a reliable and valid manner, and this goal has led framers of the *DSM* to tailor the diagnostic constructs themselves such that they can be assessed well. This highlights the close, reciprocal interrelations among assessment and psychiatric nosology: It is not simply the case that a disorder is drafted in a vacuum free of assessment concerns, and assessment instruments and procedures are then later developed to capture this phenomenon.

Assessment can only be as good as the constructs it is intended to assess. Although professionals have a tendency to reify diagnoses, there is little reason to believe that the *DSM-IV-TR* represents a definitive and precise characterization of psychopathology (Hyman, 2010). This point is clearly demonstrated by the revision toward *DSM-5*, which is a clear admission that the current nosology, like all others, is lacking. If an assessment instrument yields poor reliability (and thus poor validity as well), this is not necessarily indicative of poor assessment. Indeed, this could reflect poor construct validity of the diagnostic entity itself.

To illustrate the point that nosological shortcomings can masquerade as assessment failures, we will consider an example. Let us assume that premenstrual dysphoric disorder exists in nature, with a key feature of depressed mood temporally linked to the menstrual cycle, but it has not yet been identified by researchers and clinicians. Let us further assume that a hypothetical self-report questionnaire can assess all the symptoms and severity of depressed mood, with perfect reliability—that is, it can assess depressed mood without any error whatsoever. If the classification system did not include premenstrual dysphoric disorder, and instead attempted to capture it simply with a diagnosis of major depressive disorder (severity mild), this would cause myriad assessment problems with our otherwise precise questionnaire when administered to patients with premenstrual dysphoric disorder. Within a sample of depressed individuals, the three-day test-retest reliability of the questionnaire would likely be quite high—since our hypothetical questionnaire assesses current low mood with no error, fluctuations in test-retest reliability would largely reflect the variation in depressed mood over a three-day period. Within a sample of individuals with premenstrual dysphoric disorder—conceptualized as depression or dysthymia—the three-day test-retest reliability would probably be quite low. As women progressed through their menstrual cycles, the questionnaire would (accurately) produce significant low mood scores at baseline and much improved low mood scores only days later. This test-retest reliability could easily be interpreted as the questionnaire being an unreliable measure. In actuality, this assessment device was totally reliable. It was the diagnostic system's shortcoming that produced this putative failure of assessment.

We can consider a nonhypothetical example to further this point. Borderline personality disorder is defined by *DSM-IV-TR* with nine diagnostic criteria, at least five of which must be present for diagnosis. (As far as we are aware—and Krueger is a member of the *DSM-5* Personality and Personality Disorders Work Group—this threshold was set because five is more than half of nine, not because there were data to support this particular threshold.) Investigation of these criteria reveals that they are quite heterogeneous in terms of their content, including frantic efforts to avoid abandonment, identity disturbance, affective lability, feelings of emptiness, behavioral dysregulation, unstable and intense relationships, paranoid ideation and dissociation, suicidality, and anger problems. This is quite a broad range of symptom expression, and research has indicated that borderline personality disorder, as currently defined, reflects the confluence of multiple psychopathological problems. For instance, Sanislow and colleagues (2002) used confirmatory factor analysis to examine the latent structure of borderline personality disorder—that is, the underlying factors that accounted for how the diagnostic criteria related to one another—and determined that three underlying factors were present. First, a disturbed relatedness factor accounted for (co)variation of diagnostic criteria assessing unstable relationships, identity disturbance, feelings of emptiness, and stress-related paranoid ideation. Second, a behavioral dysregulation factor accounted for co(variation) of criteria for impulsivity and suicidal and self-mutilative behaviors. Finally, an affective dysregulation factor accounted for (co)variation of criteria for affective instability, inappropriate anger, and avoidance of abandonment. These factors were correlated but also unique, suggesting that three key psychopathological "currents" form the

basis for what is defined as borderline personality disorder. Another study, investigating the latent factors that account for a diagnosis of borderline personality disorder, rather than its individual criteria, indicated that at least two dimensions (a tendency to experience psychological distress and a tendency to engage in externalizing behaviors) accounted for the diagnosis (Eaton, Krueger, Keyes, et al., 2011; Eaton, Krueger, & Oltmanns, 2011).

Given that multiple factors appear to underlie the diagnostic criteria, and diagnosis itself, of borderline personality disorder, an assessment measure that captures borderline personality disorder criteria (or diagnosis) quite well might still have poor psychometric properties. In)addition to temporal issues (e.g., scores varying due to affective instability), reliability judged by internal consistency could also be quite low because of this construct's multidimensionality. It is quite possible that the items assessing affective dysregulation features would not move closely in tandem with items assessing disturbed relatedness features, yielding apparently poor internal consistency even though the assessment device is reliably measuring a (potentially problematic) diagnostic construct. Again, the putative success of the assessment device is attenuated not by its own failures; rather, the assessment device can only perform as well as the diagnostic constructs it is intended to measure. Diagnoses that are unreliable or invalid will yield unreliable or invalid assessments, no matter how precise the assessment instrument and procedure may be.

Three Assessment Considerations

We have detailed earlier how the classification of a disorder and its assessment are inextricably linked. We now turn our attention to three other major considerations that can affect assessment. First, we discuss comorbidity of depressive disorders. Second, we discuss how disorders present across various subpopulations, such as cultural groups. Third, we discuss how psychometric properties, such as how items of an assessment battery function, can vary nontrivially.

Comorbidity

As we discussed earlier, differential diagnosis of the depressive and related disorders can be a vexing problem for psychological classification. This picture is complicated by the fact that individual disorders do not always occur one at a time. So, in addition to assessing whether major depressive disorder *or* generalized anxiety disorder is present, the assessor must also determine whether major depressive disorder *and* generalized anxiety disorder (*and* dysthymic disorder, etc.) are present. Indeed, comorbidity is often the rule rather than the exception, and *DSM-IV-TR*'s exclusion criteria (e.g., ruling out major depressive disorder once a manic episode has occurred) often do little to minimize this overlap in terms of assessment.

One would expect some disorders to co-occur randomly given their prevalence rates. For instance, one study of a representative sample found that the past-year prevalence rates for major depressive disorder and generalized anxiety disorder were 13.3% and 2.7%, respectively. If these disorders occurred independently, one would predict, based on these prevalence rates, that four individuals out of 1,000 (i.e., 0.133 * 0.027. * 1,000 = 3.591, rounding up to 4) would have comorbid major depressive disorder and generalized anxiety disorder (Eaton, South, & Krueger, 2010). However, investigation of the actual level of overlap revealed a different pattern: 17 individuals out of 1,000 actually had this comorbid presentation. Thus, the level of disorder co-occurrence was more than 400% higher than that expected by chance, suggesting high levels of *systematic* comorbidity.

Depressive disorders can occur comorbidly with nearly every other form of psychopathology in an unsystematic way, with the overlap arising solely out of random co-occurrence reflecting prevalence rates. When one looks at the empirical data, though, clear patterns emerge. It is not the case that comorbidity of depressive disorders is unsystematic and random. Rather, the depressive disorders most commonly co-occur with each other and also with the anxiety disorders (Kessler, Chiu, Demler, & Walters, 2005; Krueger, 1999; Krueger & Markon, 2006; Mineka, Watson, & Clark, 1998; Slade & Watson, 2006; Vollebergh et al., 2001; Watson, 2005, 2009). Research in this field of structural psychopathology has indicated that the depressive disorders and anxiety disorders share a common underlying structure, which accounts for their frequent co-occurrence. This latent construct is referred to as *internalizing* and can be thought of as a dimensional liability to experience unipolar mood and anxiety pathology (e.g., generalized anxiety disorder, posttraumatic stress disorder, panic disorder, agoraphobia).

In clinical assessment, the goal is to divide variation in the depressive disorders into two parts. In classic test-theory terms, these are the true score and the error, which are equivalent to the signal and the noise. Clinical assessment of depressive disorders

attempts to capture and maximize the signal (true score) while decreasing the noise (error). The structural psychopathology research that yielded the presence of the internalizing liability, however, suggests that variation of the depressive disorders can be parsed into two other parts: common variance and unique variance. Common variance here would be internalizing itself—the variation shared by the depressive (and anxiety) disorders. It forms the core of all depressive pathology. Unique variance, on the other hand, is what makes each disorder separate from the others. It is the variation that makes major depression different from, say, dysthymia. Unique variation of one disorder does not overlap with unique variation of another disorder by definition. Unique variance also includes error. This error could be error associated with the assessment process, or it could also represent classification error as well. Insofar as some of a disorder's diagnostic criteria are relatively unrelated to core construct of the disorder, they could also be conceptualized as error in this way.

The structural psychopathology literature leaves us with an important question: What should be the focus of our assessment? Should we use a disorder-focused assessment approach that attempts to maximize the signal of each disorder, minimize the noise present in the assessment, and allow us to differentiate *DSM-IV-TR* constructs from one another in a highly precise manner? If the goal of assessment is *DSM-IV-TR* differential diagnosis, say, for reimbursement purposes, then the answer may be yes. Should we, instead, focus on assessing what appears to be at the core of the depressive disorders—the internalizing liability that is at the heart of the unipolar mood and anxiety disorders? For purposes other than differential diagnosis, the answer to this question may be affirmative in some cases. Although internalizing liability continues to be investigated actively, many studies have supported its role as important in understanding, assessing, and conceptualizing psychopathology. It accounts for lifetime patterns of comorbidity of the mood and anxiety disorders (Kessler et al., 2011). It arises primarily from genetic mechanisms (Hettema, Neale, Myers, Prescott, & Kendler, 2006; Kendler, Prescott, Myers, & Neale, 2003; Kendler et al., 2011), giving insight into the origins of these disorders. It accounts for why many disorders respond to similar psychotherapeutic (Nathan & Gorman, 2007) and pharmacological (Goldberg, Simms, Gater, & Kreuger, 2011) treatments, and it has prompted the development of transdiagnostic treatment modalities that can conceivably affect multiple disorders simultaneously by addressing their internalizing core (Barlow et al., 2011). Further, it appears increasingly likely that the *DSM-5* organization (referred to as its "meta-structure") will be organized in such a way that internalizing disorders are grouped proximally, emphasizing their close empirical connections (Andrews et al., 2009; Regier, Narrow, Kuhl, & Kupfer, 2011).

When the model of mental disorders characterized in the *DSM-IV-TR* and other recent editions is tested empirically, it tends to be inferior to the internalizing model discussed earlier (for reviews, see Eaton et al.,, 2010; Krueger & Markon, 2006). For instance, if depressive disorders are grouped together and anxiety disorders are grouped together—as they are in *DSM-IV-TR*—in a statistical testing framework (e.g., confirmatory factor analysis), this yields a poorer fit to actual observed data than the internalizing model, where these disorders are modeled such that they all relate to a single, underlying core. This is another indication that clinical assessment of depressive disorders might benefit from including assessment of internalizing liability itself in addition to more traditional disorder-specific assessment. It may be the case that the unique variance of each disorder is not worthwhile for a given purpose and may be associated with error; if that is the case, assessment of internalizing liability would be more clinically informative than disorder-specific approaches.

At this point, it is important to note that, while internalizing liability appears to hold promise as a means to classify and conceptualize psychopathology, the nature of this liability has yet to be fully characterized. Most studies of the comorbidity of depressive and anxiety disorders have conceptualized internalizing liability as a continuous dimension, ranging from very low to very high. Every individual occupies some position along this continuum. However, internalizing liability does not always emerge as a unidimensional construct. Although many studies have assumed internalizing liability is best conceptualized as a single dimension (Eaton, Krueger, & Oltmanns, 2011; Fergusson, Horwood, & Boden, 2006; Krueger et al., 1998), others have used alternative conceptualizations. For instance, some studies have found evidence that internalizing liability is actually a higher-order dimension, which subsumes two subdimensions: (1) distress (also termed anxious-misery), which is a liability primarily to major depressive, dysthymic, and generalized anxiety disorders, and (2) fear, which is a

liability primarily to social phobia, specific phobia, and panic disorder (Eaton et al., 2012; Krueger, 1999; Slade & Watson, 2006; Vollebergh et al., 2001). Other studies have conceptualized internalizing liability as a set of liability classes—that is, not as dimensional—as well (W. W. Eaton et al., 1989; Ferdinand, de Nijs, van Lier, & Verhulst, 2005; Fergusson, Horwood, & Lynskey, 1993; Kessler et al., 2005; Vaidynathan, Patrick, & Iacono, 2010; Wadsworth et al., 2001), although this is beyond the scope of the present chapter.

It is presently unclear which of these models—the unitary internalizing liability versus the higher-order, bifurcated internalizing liability—is superior, and they have rarely been compared directly. Comparisons thus far have produced equivocal results by and large (e.g., Seeley et al., 2011), likely because even when distress and fear emerge as separable aspects of a broader internalizing domain, they are very highly correlated. It may well be the case that the superiority of one model or another will depend on the goals of the clinician or researcher. What does appear to be the case, though, is that assessment of internalizing liability as a single dimension is likely adequate for most clinical purposes at this time, particularly given the highly correlated nature of the distress and fear subliabilities. (If one were to assess subliabilities, it would appear that the distress subliability would be most germane to depressive disorder assessment.)

How can an interested clinician or researcher assess internalizing liability? Because this area of structural psychopathology research is relatively new in many ways, there has been relatively little effort made toward creating assessment devices that can characterize internalizing liability well. This stands in marked contrast to *externalizing* liability—the tendency to experience antisocial personality disorder, conduct disorder, and substance abuse/dependence—where efforts have been made to develop appropriate assessment measures to capture the full range of this liability dimension (Markon & Krueger, 2005; Krueger, Marcon, Patrick, Benning, & Kramer, 2007). Researchers are only now turning their attention to means by which internalizing can be assessed. The picture is complicated, however, by the fact that internalizing liability has been identified as a latent construct in multivariate statistical analyses. Thus, while these investigations have demonstrated the presence of internalizing liability, translating these findings into practical assessment strategies is another question entirely.

One possibility of assessing internalizing liability is through questionnaires, both self- and informant-report questionnaires, developed out of the work of Achenbach beginning decades ago (e.g., Achenbach & Edelbrock, 1978, 1984). Over the years, this work focused on such measures as the Child Behavior Checklist (CBCL), and it has subsequently been expanded to include assessment of psychopathology across the adult lifespan as well. The Adult Self-Report (ASR) and Adult Behavior Checklist (ABCL) measures has national norms for ages 18 to 59 years, and the Older Adult Self-Report (OASR) and Older Adult Behavior Checklist (OABCL), which was designed for individuals aged 60–90+ years. These measures include assessment of broadband internalizing scores (a combination of depressive and anxious symptomatology), and norms provide benchmarks for comparison of a given individual with the broader population. Together, these measures and others compose the Achenbach System of Empirically Based Assessment (ASEBA), which is available at http://www.aseba.org.

A recently designed inventory, the Inventory of Depression and Anxiety Symptoms (IDAS) also appears to hold significant promise in assessing internalizing-related constructs (Watson et al., 2007). The IDAS assesses the symptoms of major depressive disorder as well as anxiety disorders. Through factor-analytic results, the authors investigated the structure of these symptoms, and the final IDAS self-report instrument emerged. The IDAS (1) measures a general factor (cf. internalizing), (2) has two broader scales, general depression, and dysphoria, and (3) has 10 specific symptom scales to investigate particular manifestations of symptomatology. These scales are suicidality, lassitude, insomnia, appetite loss, appetite gain, ill temper, well-being, panic, social anxiety, and traumatic intrusions. These broad and fine-grained characterizations of internalizing symptomatology, coupled with the instrument's good psychometric properties, make the IDAS a worthwhile measure to consider for assessment of the depressive and related disorders.

Another possible way to assess internalizing liability is to examine related scales in other measures. One such possible measure is the MMPI-2. Two scales on the MMPI-2 appear to capture internalizing liability to varying degrees. First, the PSY-5 scales, originating in the work of Harkness (Harkness & McNulty, 1994; Harkness, McNulty, & Ben-Porath, 1995), include a Negative Emotionality

Scale, which is closely linked to internalizing liability. In addition, the Restructured Clinical Scales demoralization scale RCd (Tellegen et al., 2003) also seems related to internalizing liability. The RCd was created to minimize the levels of overlap among the standard clinical scales by removing common variance, which was labeled "demoralization." Thus, RCd represents a negativistic tendency to endorse items reflecting pathology, which may be related to internalizing liability, although the strength of the association between internalizing liability MMPI-2 Restructured Clinical Scale demoralization needs to be addressed analytically by subsequent research. Finally, one measure that appears to tap into internalizing liability/negative emotionality is the Schedule for Nonadaptive and Adaptive Personality (SNAP; Clark 1993). The SNAP, a measure of personality strengths and weaknesses, has a higher-order three-factor structure of negative emotionality, positive emotionality, and disinhibition. Negative emotionality subsumes scales of negative temperament, manipulativeness, mistrust, aggression, self-harm, eccentric perceptions, and dependency, and it appears likely to tap into key aspects of internalizing liability.

A final way to assess internalizing liability is the use of measures of normal (nonpathological) personality. Recent research has demonstrated that internalizing liability is correlated almost perfectly with trait neuroticism (Griffith et al., 2010). Trait neuroticism (also referred to as negative emotionality, negative affectivity, or, when scores are reflected, as emotional stability) plays a prime role in both Big Five and Giant Three personality measures, and it is, thus, easily assessed via widely available measures. For instance, neuroticism, extraversion, conscientiousness, agreeableness, and openness to experience constitute the higher-order factors of the Five-Factor Model of personality, instantiated in the NEO-PI-R (Costa & McCrae, 1992). Another normal personality model that could be used to capture this aspect of internalizing liability is the Multidimensional Personality Questionnaire (MPQ; Tellegen, 2000), which has higher-order factors of negative emotionality, positive emotionality, and constraint. A third, and, historically, highly influential personality model was developed by Eysenck (1967, 1969, 1970; Eysenck & Eysenck, 1991). Comprising factors of extraversion, neuroticism, and psychoticism, measures assessing the Eysenckian personality model, and particularly the component of trait neuroticism, can likely be used as a reasonable proxy for internalizing liability.

To summarize, a primary assessment concern with the depressive and related disorders is comorbidity. The frequent co-occurrence of these disorders complicates assessment. Assessors conducting differential diagnosis must determine how best to map the presenting signs and symptoms into a *DSM-IV-TR* diagnosis—or into multiple appropriate diagnoses. This may be the best approach for many clinical and research applications. If the assessor is not bound by the *DSM-IV-TR* diagnostic entities, though, an alternative approach is to recognize that their comorbidity seems to reflect a coherent underlying liability dimension. This internalizing liability dimension then manifests as particular signs and symptoms, perhaps due to environmental influences. Although no gold-standard assessment of the internalizing liability dimension has yet been agreed upon, various measures of closely related constructs exist. Ultimately, the end purpose of the assessment should direct the assessment procedure and measures selected. A complete assessment of the depressive disorders, however, would likely comprise assessing for the presence/absence of the *DSM-IV-TR* diagnostic constructs and also characterizing a given individual's level of underlying internalizing liability to experience various forms of unipolar mood and anxiety psychopathology.

Subpopulations and presentation

DSM-IV-TR defines the depressive disorders generally in a "one size fits all" rubric. The polythetic criterion system, where X of Y diagnostic criteria must be present to render a diagnosis, allows for some flexibility in disorder presentation; however, the core constructs enshrined in the diagnostic manual are relatively set. In terms of clinical assessment, if a given disorder fits a given patient's symptomatology well, this is a nonissue. If, on the other hand, a patient's presentation of depressive symptomatology does not fit well into the defined disorders—typically requiring a not-otherwise-specified diagnosis—problems arise. This is a particularly salient concern when it comes to changing psychopathological manifestations across subpopulations. We now turn our attention to two subpopulation-related presentation issues with significant implications for assessment of depressive disorders: (1) culture-bound syndromes that seem to reflect some depressive symptomatology, and (2) how *DSM-IV-TR* diagnostic construct-related entities manifest differently across different population groups.

We first turn our attention to culture-bound syndromes. *DSM-IV-TR* lists a variety of culture-bound

syndromes in its Appendix I. These forms of psychopathology are "recurrent, locality-specific patterns of aberrant behavior and troubling experience that may or may not be linked to a particular *DSM-IV* diagnostic category" (p. 898). (This is opposed to the *DSM-IV-TR* primary diagnoses, which the document states have presentations that can be found worldwide.) Some of the culture-bound syndromes included in *DSM-IV-TR* show clear links to the depressive disorders, and they highlight how being mindful of cultural considerations is critical when assessing these disorders.

The culture-bound syndrome of *brain fag*, for instance, can resemble depressive disorders. When confronted with educational challenges, some high school or university students in West Africa may report its symptoms, which are conceptualized as relating to brain fatigue. Problems with thinking, concentration, and memory may be present. Another culture-bound syndrome, *ghost sickness*, resembles the depressive ideation seen in major depressive disorder, dysthymic disorder, depressive personality disorder, and bereavement. In this disorder, primarily seen in Native American individuals, individuals are often preoccupied with the deceased and death, and they may experience bad dreams, loss of appetite, weakness, fear, anxiety, confusion, and feelings of futility. *Nervois*, a form of distress seen in Latinos, can include emotional distress, sleep problems, irritability, easy tearfulness, and inability to concentrate. In China, the culture-bound syndrome *shenjing shuairuo* presents with several symptoms relating to the depressive disorders, including concentration difficulties, sleep disturbances, memory problems, sexual dysfunction, irritability, and feelings of mental fatigue.

Culture-bound syndromes can be considered to be unique forms of psychopathology that manifest within a given subpopulation and/or locale, as opposed to the *DSM-IV-TR* primary disorders, which are defined as broadly applicable across subpopulations. However, is it necessarily the case that a disorder, such as major depressive disorder, actually presents similarly across subpopulations? The answer appears to be no. Rather, the general constructs enshrined in *DSM-IV-TR*, such as depression, may manifest differently across subpopulations. This causes notable challenges for assessment of depressive and related disorders across cultures.

There is a large literature regarding cross-cultural psychopathology, and we will not belabor this discussion. Given the breadth of subpopulations globally, such a review is beyond the scope of any chapter, particularly when subpopulations can be defined in so many ways. For instance, broad ethnic groups, such as Hispanics/Latinos may show different disorder presentations from other groups; within ethnic groups, there may be meaningful differences as well, such as between Hispanics/Latinos in the United States versus South American versus the Caribbean. Thus, although our discussion up to this point has focused mostly on the importance of "big picture" assessment issues, and, in particular, on how the very nosological definition of disorders impacts assessment and comorbidity, it is just as critical to consider assessment challenges at the local level.

An example may be instructive to highlight the role of subpopulations in disorder presentation and the resulting assessment concerns. In a review, Leong, Okazaki, and Tak (2003) addressed the topic of assessment of depression in East Asia. There is some evidence that depression in East Asian cultures may express differently than in, say, the United States. In particular, there is some debate about whether the psychobiological state that manifests as major depression in the United States may manifest in a more somatic way in some East Asian cultures. As the authors detail, however, these manifestations, and proper assessment thereof, may differ nontrivially between Chinese, Korean, Japanese, and other East Asian cultures. For instance, one study of three groups of patients with depressive and related disorders—(1) Koreans living in Seoul, (2) Korean Chinese, and (3) Chinese individuals living in Yanbian, China—showed different manifestations of these disorders (Kim, Li, & Kim, 1999). This is notable for clinical assessment purposes, because patterns of symptom endorsement on the same instrument, a translated version of the Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961; Beck, Steer, & Brown, 1996; Han et al., 1986, in Leong, Okazaki, & Tak, 2003), differed across groups. The Korean patients experienced more affective symptoms, the Chinese patients experienced more somatic symptoms, and the Korean Chinese patients were in between the Korean and Chinese patient groups, experiencing a more mixed affective and somatic presentation. This issue illustrates how good clinical assessment of the depressive and related disorders involves more than simply selecting a reliable and well-validated instrument.

Ethnicity is not the only determiner of subpopulation characteristics, of course. Gender may

play a role as well. A classic example of gender differences in the presentation of the depressive disorders is the role of rumination, with studies consistently showing that women's depression tends to manifest with more rumination compared to men's depression, which tends to be associated with more problem-solving-focused approaches (Nolen-Hoeksema, 1987; Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008). Another critical consideration for subpopulation-related assessment issues is age. Just because a given assessment approach or measure has been shown to be reliable and valid in adults, this will not necessarily be the case in children or older adults (Balsis & Cully, 2008; Nezu et al., 2009). Although a clinician might choose to assess for major depressive symptoms in adults by using the BDI, she might be better served by using the Children's Depression Inventory (Kovacs, 1992) in a youth sample or the Geriatric Depression Scale (Yesavage et al., 1983) in a sample of older adults. These can be thought of as cohort differences in a cross-sectional assessment sense, an interindividual difference in manifestation based on age. However, this sort of assessment concern can also be viewed in a longitudinal sense as an intra-individual difference in manifestation based on age. The latter scenario would be an example of heterotypic continuity (Caspi & Bem, 1990; Kagan, 1969), where the depressive/internalizing liability within an individual would remain relatively constant over time but manifest differently as the individual ages. So, while assessment must be concerned with subpopulation members of individuals being assessed, one must also be concerned with a given individual's transition between subpopulation groups across the lifespan.

Psychometric issues

Certainly, psychometric issues are among the most pressing considerations when conducting assessment of depressive disorders. As noted repeatedly earlier, the reliability (including test-retest and internal consistency) of assessment devices and procedures, and the validity of the inferences drawn from these assessments, are crucial to good assessment. Given the widespread appreciation of these psychometric issues, we will not discuss them here but, instead, will refer readers to any number of canonical texts on this issue (e.g., Crocker & Algina, 2006; Lord & Novick, 1968). Instead, we will note briefly two related issues that are less frequently discussed, particularly in applied clinical settings.

First, the way that depressive disorders are defined by *DSM-IV-TR* suggests generally that diagnostic criteria contribute similarly to diagnosis. An exception can be found in the diagnostic criteria for a major depressive episode, where two criteria, depressed mood and anhedonia, are given special status in that one or both must be present for a diagnosis, making the presence of one or both necessary but not sufficient for diagnosis. Beyond this caveat, however, all nine of the diagnostic criteria contribute equally toward determination of the presence of a major depressive episode. By this polythetic approach, feelings of worthlessness and a depressive suicide attempt each count as one criterion present (toward the diagnostic benchmark of five or more), but so do insomnia and psychomotor agitation. For diagnostic assessment that is wholly compliant with *DSM-IV-TR*, each criterion must thus be assessed with similar rigor. For clinical purposes, however, given limited resources and time, it may not always be possible or even preferable to take such an approach. Characterizations of worthless feelings or suicidality often do (and likely often should) take precedence over characterizations of sleep disturbances or psychomotor changes. In this way, the clinician must be sensitive to the goals of the assessment and the determination of how critical it is that each criterion receives the same degree of consideration given their equal weight.

Second, the current polythetic criterion system includes no possibility of differential item functioning, a characteristic of test items in item response theory commonly referred to as DIF (Lord & Novick, 1968). As noted in the preceding paragraph, *DSM-IV-TR* allows each criterion to count invariably toward one "unit" of psychopathology up to the diagnostic benchmark, even though one criterion might tap into the construct being assessed more strongly than another. Not only might criteria relate differently to the construct, their relations to the construct might change across individuals or over time. For instance, adolescents often experience normal sleep duration or hypersomnia, whereas older adults often require and get less sleep nightly, which can reflect natural aging processes or insomnia (e.g., Morin, 1993). In terms of how the sleep disturbance criterion of a major depressive episode relates to the construct of interest, it may be the case that insomnia is indicative of a more significant level of depressive episode severity if it is present in a 15-year-old boy than a 90-year-old woman. This is a hypothetical example of DIF: The insomnia criteria taps more strongly into, and is more indicative of, depressivity in the younger individual than the older individual. One quality of good clinical assessment

of depressive disorders is mindfulness to such DIF issues, investigation of other potential origins of the criterion's presence, and careful application of clinical judgment to ameliorate the possibility of DIF impacting diagnoses across individuals.

Summary

We have briefly detailed some key considerations present when assessing the depressive disorders. Primary among these are definitional issues, which are associated with myriad assessment difficulties. Comorbidity is rampant, both within the depressive disorders and with related forms of psychopathology, such as anxiety disorders. To some extent, this reflects the current classification system's approach; however, it also seems to reflect a meaningful underlying liability to experience internalizing disorders. In addition, key depressive disorders may manifest differently across subpopulations, such as ethnic, gender, and age cohort groups. Similarly, some disorders with depressive features may be culture bound, thus occurring with frequency only in certain cultural groups and locales. These diversity issues complicate clinical assessment of depressive disorders, potentially attenuating the reliability and validity of a given assessment measure or protocol that performs well in other groups. Symptom endorsement may change across subpopulations, and the properties of the diagnostic criteria (and related assessment items) themselves may change. These issues clarify how good clinical assessment requires consideration of a multitude of factors beyond simple psychometrics properties of assessment measures.

General Assessment Implications

As we have seen, assessment of depressive disorders is complicated by a variety of factors, such as imprecise and arbitrary classification, definitional overlap with other constructs, differential disorder manifestation across subpopulations, and high rates of comorbidity. The primary implication of these considerations is that there is no single, circumscribed method or measure that can fully characterize depressive disorder presentation. Rather, a full assessment of depressive disorders will require several components. First, nondepressive, but related, disorders will need to be assessed to determine comorbidity patterns and to rule out particular diagnoses. Second, life events need to be examined, because certain occurrences can influence the way these disorders are conceptualized and diagnosed. For instance, giving birth prior to the onset of a major depressive episode can be indicative of a postpartum onset. Stressful life events precipitating disorder manifestation can also suggest the possibility of a nondepressive disorder, such as adjustment disorder. Third, subcultural, demographic, individual difference, and physical health variables must be investigated, given that they can have significant impacts on the presenting symptoms. Finally, a careful psychosocial history is necessary to understand the ebbs and flows of mental health over an individual's life and to appreciate manifestation patterns (e.g., seasonal affect disturbances, dysthymia versus a major depressive episode).

Assessment of all these issues can be an onerous proposition, raising the question of what the responsible clinician can feasibly do to gather relevant information. This is particularly true given that insight in depressed individuals may be biased by negativistic thinking, and this draws into question the accuracy of self-report data from patients. For example, although a nondepressed person might perceive and report relatively few stressful life events, a depressed individual may be more oriented to perceive and report them. Outside of insight-related issues, retrospective report can be biased in general (Moffitt et al., 2010).

What is a clinician to do? The answer appears to be that clinicians should conduct detailed, multimodal, multisource assessments. Thus, the clinician can assess self-reported symptoms via questionnaire and interview methods that were broad in scope and focused on multiple disorder possibilities. Behavioral observations made by the clinician, such as assessment of psychomotor slowing, attention and concentration problems, and so on, are critical. Technology can assist with such assessments as well. For example, clinicians can consider using recording devices for in vivo monitoring, having the patient wear an actigraphy device to assess diurnal behavioral activation and nocturnal sleep disturbances, and requesting the patient complete ecological momentary assessments throughout the day on a cell phone or tablet computer to gauge intraday mood lability.

Finally, information source is a critical consideration. A significant implication of the complexity of depressive disorder assessment is that patient self-report is necessary but not sufficient. Clinician-report data are also key. That said, a third, and often overlooked, data source is the informant report. Partners, friends, children, parents, coworkers, and other individuals can provide crucial supplementary information to help understand the symptomatology and history of depressive patients.

Although contacting these informants can be a time consuming endeavor on the part of the clinician, it can provide an excellent and beneficial outside perspective of the patient's functioning. One means of collecting such information without a significant time investment for the clinician is to send informant-report questionnaires by mail to informants or to send them home with the patient for distribution to appropriate informants.

Future Directions

We now turn our attention to several unresolved issues in the assessment of depressive disorders that warrant future research.

1. *What is the role of internalizing liability in assessment?* Perhaps the most critical question is how, and when, one should assess internalizing liability as part of, or in place of, a standard *DSM-IV-TR* diagnostic assessment. Because a growing number of studies indicates that internalizing liability plays a key role in the etiology, maintenance, and external correlates of depressive disorders, it seems crucial for future studies to determine (a) how to assess this liability optimally and (b) when this liability should be assessed. It may well be the case that internalizing liability accounts for the meaningful core of most depressive psychopathology, and that disorder-specific, unique variation contributes relatively little to issues of clinical importance (e.g., suicidality).

2. *How should depressive disorders be classified?* As we discussed earlier, nosology necessarily informs clinical assessment, but assessment concerns have historically had a major impact on nosology as well. As the field moves toward the finalization and publication of *DSM-5*, the changes to the depressive disorders, and the resulting changes in their assessment, will be an important area of study. First, it will be necessary to determine how the diagnostic criteria for the depressive disorders function. Do they seem to indicate coherent latent constructs or are they heterogeneous and multidimensional? Do they show varying endorsement rates across subpopulations? Second, it will be important to determine how best to assess these criteria. What items are necessary to capture the diagnostic criteria? How do these items function, particularly in a DIF sense?

3. *What are the alternative methods for assessment of depressive disorders*? The majority of clinical assessment is done via diagnostic interview and/or questionnaires, and most of the information gathered reflects solely self-report information. It is important to expand our assessment armamentarium to include informant-report information more commonly. It may well be that particular aspects of the depressive disorders (e.g., psychomotor slowing) may be more amenable to assessment by informant-report whereas other aspects (e.g., feelings of hopelessness, suicidal ideation) are more amenable to assessment by self-report. Moving beyond interviews and questionnaires will likely also be key to facilitate improvements in depressive disorder assessment long-term. Several approaches seem likely candidates to improve assessment, including molecular genetics, psychophysiological responses (e.g., event-related potentials), and structural and functional neuroimaging. The integration of such objective measures with subjective reports from patients and their informants may improve assessment broadly and also serve to integrate psychopathology research with more foundational basic science research in psychology and neuroscience.

4. *What is the role of empirically supported assessment?* Within clinical psychology over the past several decades, there has been a marked focus on the identification and application of empirically supported treatments (Nathan & Gorman, 2007). Given that intervention is underpinned by assessment, there has been a separate, but somewhat quieter, call for empirically supported assessments. Indeed, it seems that empirically supported treatments and assessments (and, likely, classification) will form the basis of the emerging clinical science movement. Empirically supported assessment is not only a question of determining whether a measure or procedure has adequate psychometric properties. It will also involve direct comparison of assessment approaches and may well lead to the determination of "gold standard" assessments for different symptom-presentation patterns, subpopulations, and so on. Although there have been notable efforts in this domain (Hunsley & Mash, 2008; Joiner, Walker, Pettit, Perez, & Cukrowicz, 2005; Klein, Dougherty, & Olino, 2005; Nezu et al., 2000), more work needs to be done to establish an empirically supported assessment battery and procedure for depressive disorders.

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CHAPTER

6 Depression and Comorbidity with Panic Disorder

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Abstract

Comorbidity between panic disorder and major depression is found in the majority of individuals with panic disorder and a substantial minority of individuals with major depression. Comorbidity between panic disorder and depression is associated with substantially more severe symptoms of each of the disorders, greater persistence of each disorder, more frequent hospitalization and help-seeking behavior, more severe occupational impacts, and a significantly higher rate of suicide attempts. These two disorders share many risk factors, such as neuroticism, exposure to childhood abuse, informational processing biases, and elevated amygdala activation in response to negative facial expressions. Research on the temporal priority of panic disorder and major depression has most frequently found that panic attacks and other symptoms of anxiety predate the onset of the first major depressive episode, but the first depressive episode predates the onset of full panic disorder. Treatment studies indicate that cognitive behavioral therapy (CBT) is the most effective treatment for panic disorder. Other forms of treatment include medication, particularly selective serotonin reuptake inhibitors. Comorbid depression does not appear to affect the outcome of CBT for a principal diagnosis of panic disorder, and CBT for panic disorder has positive, yet limited, effects on symptoms of depression.

Key Words: panic disorder, panic attacks, major depression, comorbidity, cognitive behavioral therapy

Introduction to Specific Comorbidity Issues

Comorbidity between panic disorder and depression is one of the strongest psychiatric comorbidities and the most frequent form of anxiety and mood disorder comorbidity in both treatment samples (Clayton, 1990) and general population studies (Merikangas et al., 1996). Comorbidity between these two disorders has been consistently associated with greater symptom severity and impairment (Brown, Schulberg, & Shear et al., 1996), disability (Hegel et al., 2005), more suicide attempts (Johnson, Weissman, & Klerman, 1990), and poorer treatment response (Brown, Schulberg, Madonia, Shear, & Houck, 1996; Brown, Schulberg, & Shear 1996; Walker et al., 2000) when compared to either panic disorder or depression alone. Theoretical debate has often centered on whether these two highly comorbid disorders represent one severe condition (Gorman & Coplan, 1996; Noyes et al., 1990; Roy-Byrne et al., 1992), or two co-occurring disorders with separate etiological underpinnings (Dolan, Bench, Brown, Scott, & Frackowiak, 1994; Nordahl et al., 1990). Research devoted to disentangling these two theories has focused on temporal onset of the disorders, similarities and differences in neurobiological substrates, heritability, and environmental stressors associated with each disorder. As the co-occurrence of these two disorders leads to greater symptom severity and persistence, impairment, and higher risk of suicidal

and harmful behaviors, it is imperative for clinicians to assess for the presence of comorbidity given the significant implications for the direction and course of treatment.

Definitions of the Disorders and of Comorbidity

Panic attacks are discrete episodes characterized by an abrupt surge of intense fear or discomfort that reaches a peak within minutes and during which time four or more (of 13) physical and cognitive symptoms occur, such as rapid heart rate, shortness of breath, and fears of losing control or dying, as listed in the panic attacks checklist in the *Diagnostic and Statistical Manual of Mental Disorders* (fourth edition, text revision [*DSM-IV-TR*]; American Psychiatric Association, 2000). Panic attacks are distinguished from other forms of anxiety by their sudden onset and rapid increase in arousal, as opposed to a slow and gradual building of anxious arousal. Panic attacks that occur within panic disorder are often described by patients as unexpected, such that they occur "out of the blue" or with no apparent trigger. The diagnosis of panic disorder is given when recurrent unexpected panic attacks are accompanied by at least one month of persistent concern about future attacks and their consequences and/or significant maladaptive changes are made to behavior as a consequence of the attacks (American Psychiatric Association, 2000).

Panic disorder is often, but not always, accompanied by agoraphobia. In *DSM-IV-TR* (American Psychiatric Association, 2000), panic disorder and agoraphobia are linked and a diagnosis of agoraphobia is defined as a specific subset of diagnoses of panic disorder. However, in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 2013), panic disorder and agoraphobia are two distinct disorders that can occur independently of one another. In *DSM-IV-TR*, agoraphobia is defined by at least six months of marked fear or anxiety about at least two public or crowded environments, such as driving or being outside of the home alone, at malls, at sporting events, or in open spaces. The individual fears and/or avoids these situations because escape might be difficult or help might not be available in the event of incapacitation or panic-like symptoms. The agoraphobic situations are either avoided, require the presence of a companion, or are endured with great anxiety. Additionally, the fear associated with these situations must be disproportionate to the actual risk of danger and must cause significant distress or impairment in important areas of functioning (American Psychiatric Association, 2000).

Major depressive disorder in *DSM-IV-TR* (American Psychiatric Association, 2000) is defined by the presence of either depressed mood or anhedonia, or both, for two weeks or more. Anhedonia is defined as a markedly diminished interest or pleasure in all or almost all activities. If one or both of these symptoms is present, other symptoms assessed include a significant weight loss or gain (> 5% body weight) or an increase or decrease in appetite, significant changes in sleeping patterns such as insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or inappropriate guilt, changes in the ability to concentrate or make decisions, and recurrent thoughts of death or suicide. A total of at least five of these symptoms must be present for two weeks or longer for a diagnosis of major depressive disorder to be given.

In the literature, comorbidity between panic disorder and depression has been defined in multiple ways. Concurrent comorbidity is when both disorders co-occur at the same time, either presently or in the past. Lifetime comorbidity is when an individual has been given a diagnosis of both disorders at some point in his or her lifetime, such that the disorders may have occurred concurrently, may have overlapped at certain points in time, or may have occurred at distinctly different time points. Panic attacks that occur in the absence of a diagnosis of panic disorder are often thought to be a nonspecific severity marker of psychopathology in general (Kircanski, Craske, Epstein, & Wittchen, 2009). As a result of this status, it is unclear whether co-occurrence of panic attacks and depression should be classified as a comorbidity, and it is also unclear if it is really panic disorder that is comorbid with depression or if it is actually the presence of panic attacks that explain the comorbid relationship.

Prevalence, Impact, and Shared Risk Factors

Prevalence

Prevalence of comorbidity between panic disorder and depression is consistently high, although variable, in epidemiological, clinical, and primary care studies, with depression being present in a majority of individuals with panic disorder and panic disorder being present in a substantial minority of individuals with depression. One of the largest epidemiological studies to date, the National Comorbidity Survey (NCS), surveyed

lifetime rates of *Diagnostic and Statistical Manual of Mental Disorders* (third edition, revised [*DSM-III*]; American Psychiatric Association, 1980) disorders across 8,098 respondents in the United States with an 82.4% response rate. In the replication of this study, 12-month prevalence rates were 2.8% for panic disorder and 6.7% for major depressive disorder (Kessler, Chiu, Demler, & Walters, 2005). In the original NCS study, lifetime prevalence rates were 7.2% for panic attacks, 3.4% for panic disorder, and 16.9% for major depressive episode. About half of participants with lifetime panic attack (50.9%) and panic disorder (55.6%) also met lifetime criteria for depression, and about one fifth (21.6%) of the individuals with lifetime depression reported a lifetime history of panic attacks and one tenth (11.2%) met criteria for lifetime panic disorder (Kessler et al., 1998). However, lifetime prevalence rates should be interpreted with caution as they are often less reliable than 12-month prevalence rates and cumulative risk rates.

The odds ratios for lifetime panic with depression were found to be significant and substantial; the ratio for panic attack with depression was 6.2, and the ratio for panic disorder with depression was 6.8. In other words, it is 6.2 times more likely that an individual who experiences panic attacks will experience a major depressive episode than an individual who does not experience panic attacks, and an individual with panic disorder is 6.8 times more likely to experience a major depressive episode than an individual without panic disorder. Additionally, significant episode comorbidity, or the co-occurrence of multiple and discrete episodes of major depressive disorder and panic disorder at different points throughout the lifetime, was found among those with a lifetime history of both disorders. This finding indicates that the onset, persistence, and recurrence of one disorder are associated with the onset, persistence, and recurrence of the other (Roy-Byrne et al., 2000).

Another large-scale epidemiological study of 12,668 patients in the National Institute of Mental Health Epidemiologic Catchment Area Program indicated that 2.1% of the population studied had a lifetime diagnosis of both panic disorder and major depressive episode, while 4% had only major depression and 2% had only panic disorder (Andrade, Eaton, & Chilcoat, 1994). The prevalence of these disorders occurring together was 11 times greater than expected by chance.

Brown, Campbell, Lehman, Grisham, and Mancill (2001) examined the comorbidity of current anxiety and mood disorders in a clinical sample of 1,127 outpatients. They found that 33% of patients with a current diagnosis of panic disorder with agoraphobia had a current diagnosis of major depressive disorder and that 24% of patients with a current diagnosis of major depressive disorder had a current diagnosis of panic disorder with agoraphobia. It is important to note that panic disorder without agoraphobia was not significantly related to greater comorbidity with depression, suggesting that the interference from agoraphobia is a predominant contributor to high comorbidity rates. This finding makes clinical sense as more restrictions on an individual's mobility and the interference caused by avoidance of necessary daily activities may contribute to the development of depression, or may increase the severity of depressive symptoms, through marked impacts on the individual's quality of life. Similarly, Biederman and colleagues (2005) found that in a sample of 1,031 referred clinical patients, 58% of patients with current panic disorder had current comorbid major depression, and 12.5% of those with current major depression had comorbid panic disorder. This study did not assess differences between panic disorder with agoraphobia and without agoraphobia on comorbidity rates.

A review of clinical studies (Katon & Roy-Byrne, 1991) found that approximately 25% of currently depressed patients have a lifetime history of panic disorder, and 40% to 80% of patients with current panic disorder have experienced a major depressive episode in their lifetime.

In sum, comorbidity between panic disorder and major depression is found in the majority of individuals with panic disorder and a substantial minority of individuals with major depression. Rates of comorbidity between panic attacks and depression are even higher than between full panic disorder and depression. These findings have been consistent across varied treatment- and nontreatment-seeking samples.

Impact

The impact of comorbid panic disorder and major depression is substantial. Patients with both disorders have more severe symptoms, greater functional impairment, more anxiety and somatic concerns, increased likelihood of using multiple drug treatments, and increased risk of suicide than patients with only panic disorder or major depression (Baldwin, 1998).

According to results from the NCS study (Roy-Byrne et al., 2000), individuals suffering from

both panic attacks with comorbid lifetime major depression and major depression with comorbid lifetime panic attacks reported significantly more severe symptom ratings for the primary disorder. Furthermore, among individuals with both disorders (either lifetime or current), a significant linear association was found between the number of physiological symptoms during panic attacks and the number of depressive symptoms during depressive episodes. The NCS study also found that when looking at the effects of comorbid depression on the course of panic disorder, comorbidity was associated with greater professional help-seeking, greater perceived role impairment, greater prevalence of attempted suicide, and more recent panic attacks than in panic disorder alone. Similarly, comorbid panic disorder affected the course of depression by increasing professional help-seeking, perceived role impairment, prevalence of attempted suicide, and the number of major depressive episodes.

Findings from clinical studies have been similar. Grunhaus, Pande, Brown, and Greden (1994) compared clinical symptoms and course of illness in 119 patients with major depression alone and 57 patients with major depression and comorbid panic disorder. Compared to the depression-only group, the comorbid group experienced more severe symptoms; had higher ratings on feelings of inadequacy, somatic anxiety, and phobia; required treatment and hospital admission earlier; and required psychiatric hospitalization more frequently.

Comorbid patients have been found to have an increased rate of suicidal ideation (Fawcett, 1992; Johnson et al., 1990) and suicide attempts (Johnson et al., 1990), compared with patients with panic disorder or depression alone. Johnson et al. (1990) examined epidemiological data from the Epidemiologic Catchment Area study and found that 7% of individuals with only panic disorder and 7.9% of individuals with only major depression had attempted suicide. However, 19.8% of individuals with comorbid panic disorder and major depression had attempted suicide in their lifetime, a significantly higher number than in either disorder alone. The odds ratio comparing suicide rate for individuals with comorbid panic disorder and depression to individuals with no psychiatric disorder was 14.3, meaning that individuals with comorbid diagnoses are 14.3 times more likely to attempt suicide than those with no psychiatric disorders.

In sum, comorbidity between panic disorder and depression has been associated with the presence of more and more severe symptoms of each of the disorders, greater persistence of each disorder, more frequent hospitalization and help-seeking behavior, more severe occupational impacts, and a substantially higher rate of suicide attempts.

Shared Risk Factors

The tripartite model (Clark & Watson, 1991) has offered a great deal of insight into the relationship between anxiety and depression and their shared and unique risk factors. The tripartite model proposes that there are symptoms shared across anxiety and depression as well as symptoms unique to each. Shared symptoms typically are represented by a negative affect or general distress factor. Symptoms of anhedonia and the absence of positive affect are specific to depression whereas symptoms of physiological hyperarousal are specific to anxiety. Cox, Enns, Walker, Kjernisted, and Pidlubny (2001) compared panic disorder and major depression on dimensions of the tripartite model and found continued support for the well-researched theory, such that the shared higher order risk factor of negative affectivity, or neuroticism, and the unique factors of low positive affect and anxious arousal correctly classified over 75% of participants. However, more recent research has found that the hyperarousal factor does not sufficiently explain the heterogeneity found among anxiety disorders and, in fact, the anxious arousal factor appears to be unique to panic disorder, rather than a factor relevant to all anxiety disorders (Mineka, Watson, & Clark, 1998).

Genetic risk studies have found that psychiatric disorders largely map onto two genetic risk factors, internalizing (major depression, generalized anxiety disorder, phobias) and externalizing disorders (alcohol and substance abuse, antisocial personality disorder, conduct disorder; Kendler, Prescott, Myers, & Neale, 2003). Within the internalizing disorders, two genetic factors predispose individuals to disorders characterized by anxious-misery (major depression, generalized anxiety) or fear (phobias; Kendler et al., 2003). From these data, large-scale genetics studies have further investigated the shared genetic risk among internalizing disorders and found that the factors affecting genetic variation between panic disorder (as well as other anxiety disorders) and major depressive disorder largely reflect the same factors affecting variation in neuroticism (Fanous, Gardner, Prescott, Cancro, & Kendler, 2002; Hettema, Prescott, & Kendler, 2004).

In a study of 9,000 twin pairs, Hettema, Neale, Myers, Prescott, and Kendler (2006) found that genetic factors shared with neuroticism accounted

for between one third and one half of the genetic risk across the internalizing disorders, which included major depression, panic disorder, generalized anxiety disorder, and the phobias. However, they also found that neuroticism did not capture all the genetic variance underlying the internalizing disorders. A second, neuroticism-independent, common genetic factor was identified that accounted for a proportion of the genetic variance for the non-phobic internalizing disorders (major depression, generalized anxiety disorder, and panic disorder) that was similar to the proportion accounted for by the neuroticism-related common genetic factor. These results show that panic disorder and major depression share a great deal of genetic variability, partially attributable to shared genetic predispositions to neuroticism and partially due to a separate genetic factor that is separate from neuroticism and not entirely elucidated yet.

Exposure to childhood physical and/or sexual abuse is also a shared risk factor between panic disorder and depression. In a 21-year longitudinal study, Goodwin, Fergusson, and Horwood (2005) found that young people exposed to physical abuse had odds of panic disorder that were three times higher than for those not exposed to physical abuse. Similarly, those reporting childhood sexual abuse had odds of panic disorder that were 2.2 times higher. These results confirmed the findings of many previous studies that did not have access to longitudinal data (e.g. Safren, Gershuny, Marzol, Otto, & Pollack, 2002; Stein et al., 1996). Similarly, childhood physical and sexual abuse is a significant risk factor for depression, such that adolescents and young adults who experienced childhood abuse were three times more likely to develop major depression than those who were not abused (e.g., Brown, Cohen, Johnson, & Smailes, 1999).

An extensive body of research has evaluated information-processing biases in relation to anxiety and depression. It is not fully clear whether these biases serve as risk factors for the development of anxiety and mood disorders or whether they develop as a consequence of the disorders themselves. Research on attentional and information processing biases has focused largely on anxiety disorders and unipolar depression as a whole and less specifically on panic disorder; however, it is still useful to note that such biases appear to be associated with both forms of disorders, in slightly different ways.

Only a few studies have directly compared anxiety and depression in terms of information-processing biases. In one study directly comparing panic disorder to depression (Carter, Maddock, & Maggliozi, 1992), the panic disorder group showed a significant interference in color naming of supraliminal threat words (presented on cards), as well as depression words, whereas the depressed group did not. In another study, faster eye movements toward threatening faces were observed in generalized anxiety disorder than a depressed group, most of whom had comorbid generalized anxiety disorder as well (Mogg, Millar, & Bradley, 2000). Finally, depressed patients showed an attentional bias to sad facial expressions presented for 10,000 ms, whereas patients with generalized anxiety disorder did not show an attentional bias to sad, angry, or happy faces (Gotlib, Kraspernova, Yue, & Joormann, 2004). Clearly, conclusions are limited from so few studies.

Still, Mathews and MacLeod (2005) concluded that depression is characterized by selective attention to cues that are consistent with negative affect when presented at long durations of one second or more (e.g. Gotlib et al., 2004), suggesting the involvement of strategic control processes. In contrast, only anxiety is characterized by selective attention to threat cues at shorter durations of 500 ms or less and under masked conditions (Mogg & Bradley, 2002), suggesting that selective attention toward threatening cues represents a more automated process, not dependent on conscious awareness in anxiety disorders. These conclusions were drawn from studies that focused on either all anxiety disorders or specific anxiety disorders, including panic disorder. Conceivably, the information-processing features support threat sensitivity in persons with anxiety disorders, whereas they support deeper evaluation and rumination in persons with depression. Finally, both anxiety and depression are associated with appraisal biases, to interpret ambiguous information in a negative fashion, albeit more threat laden in anxiety disorders (e.g. Eysenck, Mogg, May, Richards, & Mathews, 1991) and more negative self-evaluation in depression (e.g. Lawson & MacLeod, 1999).

The amygdala plays a critical role in threat assessment, in forming associations regarding danger in the environment, and in mediating response to threat or potential threat via descending projections to regions that mediate autonomic responses (e.g., heart rate, blood pressure, respiration, sweating, etc.), and abnormal amygdala functioning has been observed and implicated as a risk factor for or consequence of anxiety disorders (see Craske et al., 2009 for review).

This line of research has found that both anxious (Blair et al., 2008) and depressed (Sheline et al., 2001) individuals show an elevated amygdala response when viewing negative facial expressions, suggesting that abnormalities in amygdala function could mediate symptoms of abnormal threat assessment, exaggerated fear responses, and abnormalities in learning about the dangers of environments (Craske et al., 2009). However, specific aspects of amygdala function may distinguish between anxiety disorders and depression. Some findings suggest that anxiety disorders may be preferentially characterized by right-lateralized amygdala function (Fredrikson & Furmark, 2003) whereas depression is characterized by left-sided amygdala function, which may reflect lateralized aspects of normal amygdala function in humans (Wright et al., 2001). Further, elevated resting metabolism within the amygdala has been consistently found in depression but not in anxiety disorders (Drevets, 2003). These studies were completed using a mix of different anxiety disorders, including panic disorder; however, more studies are needed that directly examine shared effects of panic disorder and depression.

In sum, panic disorder and major depression share many risk factors, most predominantly the personality trait of neuroticism, or the vulnerability to experiencing negative affect, which has been found consistently in both phenotypic and genetic research. Other shared risk factors include exposure to childhood abuse, informational-processing biases, and elevated amygdala activation in response to negative facial expressions.

Issues of Temporal Priority, Development, and Cause and Effect

Temporal Priority

Research on the temporal priority or the timing of onset of panic disorder and depression indicates that the age of onset of each disorder is variable. In the NCS study (Kessler et al., 1998), retrospective age-at-onset reports were compared to assess the temporal priority of first onsets of panic attacks, panic disorder, and depression. Among the 302 respondents who reported at least one lifetime panic attack and one lifetime episode of depression, 31.1% stated that their first episode of depression occurred prior to their first panic attack, 25.5% stated that their first episode of depression and first panic attack occurred in the same year, and 43.4% said their first panic attack occurred at an earlier age than their first depressive episode. Among respondents with comorbid lifetime panic disorder and depression, where age of onset of panic disorder was defined as the first cluster of four panic attacks or the first month of consistent worry about panic attacks, 48% reported that depression began at an earlier age than panic disorder, 30.6% reported that both disorders started in the same year, and 21.5% said that panic disorder started at an earlier age than the first depressive episode.

These results appear to be at odds with previous literature that has consistently found anxiety to predate depression in individuals with lifetime comorbidity (e.g., Hagnell & Grasbeck, 1990; Lydiard, 1991). However, when anxiety disorders are analyzed in the aggregate, the NCS data find the same results, as early-onset phobias are typically the temporally primary disorders in this group. The NCS study also found that at least half of respondents with comorbid panic disorder and depression have at least one other prior anxiety disorder, which suggests that panic disorder and depression may be part of a larger anxious-depression syndrome in which another anxiety disorder is temporally primary. Different definitions of panic onset also lead to variable results. If the onset of panic is defined as the occurrence of the first panic attack, then panic occurring before depression is slightly more common, whereas when the onset of panic is defined as the age of onset of panic disorder, then depression occurring before panic disorder is more common.

In their clinical sample, Stein, Tancer, and Uhde (1990) found similar results as the NCS study, although they did not examine anxiety disorders as an aggregate. That is, among those with current comorbid panic disorder and depression, 63% reported a depressive episode before the onset of panic disorder, while 38% experienced their first depressive episode secondary to the development of panic disorder. This study also did not separate the first occurrence of panic attack from the development of panic disorder, leaving it unclear if the rate of depression preceding panic symptoms may be smaller if the onset of panic symptoms was defined as first occurrences of panic attacks.

One line of research has examined the presence of panic attacks, without a full diagnosis of panic disorder, as a specific risk factor for the subsequent development of depressive episodes. Goodwin, Fergusson, and Horwood's (2004) 21-year birth cohort study conducted in Christchurch, New Zealand, found that panic attacks in the preceding three years increased the risk for developing a current major depressive episode among young adults, after controlling for early behavioral risk factors for

psychopathology such as past history of depression, childhood abuse, and personality characteristics. In the prospective Early Developmental Stages of Psychopathology study, covering up to age 30, Goodwin, Lieb, et al. (2004) found that primary panic attacks were associated with increased risk for incident major depression with an odds ratio of 2.8. Finally, in a 10-year prospective longitudinal examination of the same data set by Beesdo and colleagues (2007), the occurrence of panic attacks in individuals with social anxiety disorder (i.e., cued panic in social situations) increased the risk for subsequent depression. This study did not evaluate unexpected or uncued panic attacks separate from social anxiety disorder.

Development

Research on the development of comorbid panic disorder and depression has often focused on whether patients with both disorders actually have two separate and co-occurring disorders or one disorder that marks a more severe condition. Evidence for the theory that comorbidity represents one severe disorder comes primarily from studies of biological similarities of patients with panic disorder and depression. Such studies have found shared disturbances of the hypothalamic-pituitary-adrenal axis function, serotonergic neurotransmission, thyroid releasing hormone, and growth hormone (see Stein & Uhde, 1990, for review). However, more recent neuroimaging studies, whose measures have stronger sensitivity and specificity than the previously used biological measures, indicate that panic disorder and depression have substantially different neurobiological substrates (i.e., Dolan et al., 1994; Nordahl et al., 1990).

Corroborating evidence for the theory that these disorders represent two distinct phenomena comes from family studies that have sought to determine whether panic disorder and depression aggregate separately or together in families. These studies have found that comorbid panic disorder and depression does not aggregate separately from pure panic disorder and pure depression (Maier, Minges, & Lichtermann, 1995; Weissman et al., 1993), indicating the specific and independent transmission of each disorder and the separation of panic disorder from depression as a distinct disorder.

Cause and Effect

Examination of the underlying causes of comorbidities in the NCS study (Kessler et al., 1998) yielded mixed results, raising questions of whether causes of comorbidity differ depending on which disorder is temporally primary. When depression occurs prior to panic attacks, if the depression has remitted before the development of panic attacks or disorder, the presence of a past depressive episode does not affect the course or severity of the panic. This is consistent with findings from clinical studies that past depressive episodes that have remitted do not affect the severity of current panic attacks or panic disorder (Lesser, Rubin, Pecknold, & Rifkin, 1988; Maddock et al., 1993). This result, taken with another finding that the number of depressive symptoms increases the risk for subsequent panic attacks, suggests that temporally secondary panic may serve as a severity marker for depression rather than a comorbid condition.

When panic is temporally primary, it is unclear whether panic attacks represent a causal factor in and of itself or if it represents a proxy for another underlying causal factor. This discrepancy is based on the finding that respondents with a history of panic attacks have the same elevated risk of later depression regardless of whether their panic is active or in remission, which can be interpreted multiple ways. First, it could be that panic causes depression through the consequences of panic that persist after the remission of panic attacks, such as avoidance, secondary agoraphobia, and secondary substance abuse. It is also possible that panic attacks are a marker of some cluster of risk factors that is associated with both panic disorder and depression. Regardless of the interpretation, the results point to the fact that individuals with a history of panic attacks are at increased risk for the development of both future panic disorder and depression.

In sum, research on the temporal priority of panic disorder and major depression is mixed and depends largely on the definitions of onset used. Most research has found that panic attacks and other symptoms of anxiety, including other anxiety disorders, typically predate the onset of the first major depressive episode but that the first depressive episode predates the onset of full panic disorder in more than 50% of cases. Developmental research shows that despite high rates of co-occurrence, panic disorder and depression appear to be two distinct disorders as they aggregate separately among families of individuals with both disorders and are associated with different neurobiological substrates.

Future Research Directions

While past research has consistently shown a very high rate of comorbidity between panic disorder and

depression, as well as the many impacts that their co-occurrence have on the symptoms and course of each disorder, there are several lines of research that would be beneficial in further elucidating the relationship between these disorders. Research on the temporal priority of each of the disorders has been mixed and has varied based on the use of different definitions of disorder onset. The question of whether it is the occurrence of panic attacks, panic disorder, or depression that develops primarily and which serves as a causal factor for the development of secondary diagnoses remains unclear. It is also common for other anxiety disorders to co-occur with panic disorder and depression, and many develop temporally earlier than either panic disorder or depression, pointing to the possibility that other forms of anxiety may serve as causal factors as well. Longitudinal research would aid in the understanding of the course from panic attacks to panic disorder and depression as well as how they each affect the development, course, and remission of each other.

Further research on the neurobiological and biological processes associated with panic attacks, panic disorder, and depression would be greatly beneficial to understanding the common and unique factors associated with the development and course of panic disorder and depression and how they affect the development and course of each other. Such research would also give further support for the current view that these two disorders represent two diagnostically distinct entities or would support previous theories that the co-occurrence of these two highly comorbid disorders represent one more severe disorder. This research should also focus on potential biological and neurobiological relationships between panic attacks and panic disorder and depression, which may explain whether panic attacks serve as a risk factor or a severity marker for these disorders. Additionally, more work is needed on the question of how much of the shared variance with depression is due to the presence of panic attacks versus panic disorder.

Finally, more research investigating dimensional constructs of panic disorder and depression is needed to be consistent with the National Institute of Mental Health's new Research Domain Criteria initiative, which calls for new ways of classifying psychopathology based on the dimensions of observable behavior and neurobiological measures. Much of the research examining the tripartite model and subsequent models of common and specific risk factors for anxiety and depression have relied primarily on self-report measures to examine constructs such as the experience of positive and negative affect, personality factors, and anxiety sensitivity. Future research should use more behavioral and neurobiological paradigms for testing the current models as well as other dimensional constructs, such as sensitivity to threat and reward, that extend beyond self-report.

Assessment and Intervention Strategies

Assessment

When assessing panic disorder in a patient with current or past major depression or vice versa, a detailed history will aid in defining the relationship between these two disorders and may yield insight into how the experience of one affects the presence and course of the other. As discussed in the Temporal Priority and Impact sections of this chapter, the order of development is variable, but each disorder appears to increase the likelihood of onset of an episode of the other and increases the severity and persistence of the symptoms. Therefore, when assessing one disorder, it is important to be aware of indicators of past and present episodes of the other.

An in-depth interview is the first step in establishing diagnostic features and the profile of symptomatic and behavioral responses. Several semi- and fully structured interviews exist. The Anxiety Disorders Interview Schedule–Fourth Edition (DiNardo, Brown, & Barlow, 1994) assesses anxiety disorders primarily as well as mood disorders and somatoform disorders.

Several standardized self-report inventories provide useful information for treatment planning, as well as being sensitive markers of therapeutic change. The Anxiety Sensitivity Index (Reiss, Peterson, Gursky, & McNally, 1986) has received wide acceptance as a trait measure of threatening beliefs about bodily sensations. It has good psychometric properties and tends to discriminate panic disorder/agoraphobia from other types of anxiety disorders (e.g., Taylor, Koch, & McNally, 1992). More specific information about which particular bodily sensations are feared the most, and what specific misappraisals occur most often, can be obtained from the Body Sensations and Agoraphobia Cognitions Questionnaires (Chambless, Caputo, Bright, & Gallagher, 1984). The Mobility Inventory (Chambless, Caputo, Gracely, Jasin, & Williams, 1985) lists agoraphobic situations that are rated in terms of degree of avoidance when alone and when accompanied.

The Albany Panic and Phobia Questionnaire (Rapee, Craske, & Barlow, 1995) assesses fear and avoidance of activities that produce feared bodily sensations, as well as more typical agoraphobia and social situations. Factor analyses confirmed three distinct factors, which have been labeled Agoraphobia, Social Phobia, and Interoceptive Fears. The Anxiety Control Questionnaire assesses perceived lack of control over anxiety-related events and occurrences, such as internal emotional reactions or externally threatening cues (Rapee, Craske, Brown, & Barlow, 1996). This scale is designed to assess locus of control but in a more specific and targeted manner relevant to anxiety and anxiety disorders when compared to more general locus of control scales.

Cognitive Behavioral Therapy for Panic Disorder

Cognitive behavioral therapy (CBT), involving most or all of the components listed in detail below, yields panic-free rates in the range of 70% to 80% and high end-state rates (i.e., within normative ranges of functioning) in the range of 50% to 70% for panic disorder with minimal agoraphobia (e.g., Barlow, Craske, Cerny, & Klosko, 1989; Clark et al., 1994). Two meta-analyses reported very large effect sizes of 1.55 and 0.90 for CBT for panic disorder (Hoffman & Smits, 2008; Westen & Morrison, 2001). Also, results generally maintain over follow-up intervals for as long as two years (Craske, Brown, & Barlow, 1991).

The components of CBT are as follows:

Education. The treatment begins with education about the nature of panic disorder, the causes of panic and anxiety, and the way in which panic and anxiety are perpetuated by feedback loops among physical, cognitive, and behavioral response systems. In addition, specific descriptions of the psychophysiology of the fight–flight response are provided, as well as an explanation of the adaptive value of the various physiological changes that occur during panic and anxiety. The purpose of this education is to correct the common myths and misconceptions about panic symptoms (i.e., beliefs about going crazy, dying, or losing control). The Education section also distinguishes the state of anxiety from the emotion of fear/panic, both conceptually and in terms of its three response modes (subjective, physiological, and behavioral). This distinction is central to the model of panic disorder and to the remainder of the treatment.

Self-monitoring. Self-monitoring is introduced as a way of enhancing objective self-awareness and increasing accuracy in self-observation. A panic attack record is to be completed as soon after each panic attack as possible and provides a description of cues, maximal distress, symptoms, thoughts, and behaviors.

Breathing retraining. Breathing retraining became a central component early on in the development of panic-control treatments because many panic patients describe hyperventilatory symptoms as being very similar to their panic attack symptoms. In early conceptualizations, panic attacks were related to stress-induced, respiratory changes that either provoke fear because they are perceived as threatening or augment fear already elicited by other phobic stimuli (Clark, Salkovskis, & Chalkley, 1985). Several studies illustrated a positive effect of breathing retraining (e.g. Kraft & Hoogduin, 1984). However, several studies suggest that the addition of breathing retraining does not improve upon in vivo exposure alone (e.g., Schmidt et al., 2000). Given the recent recognition that tolerance of fear and anxiety may be a more critical learning experience than the elimination of fear (see Eifert & Forsyth, 2005), breathing retraining has been de-emphasized since it could become a method of avoidance of physical symptoms or a safety behavior and thereby antitherapeutic.

On the other hand, advances have been made using capnometry-assisted respiratory training (CART), which targets respiratory dysregulation, in particular reduced levels of carbon dioxide in the blood that can result from hyperventilation (Meuret, Wilhelm, Ritz, & Roth, 2008). CART is a four-week training program that uses immediate feedback of end-tidal PCO_2, or the partial pressure of carbon dioxide present after exhalation, to teach patients how to raise their subnormal levels of PCO_2 (hyperventilation) and thereby gain control over dysfunctional respiratory patterns and associated panic symptoms (e.g., shortness of breath, dizziness). CART substantially differs from traditional breathing retraining because it focuses directly on the proposed mediator of the relationship between breathing dysregulation and panic, PCO_2 (see Meuret, Wilhelm, Ritz, & Roth, 2003, for review).

Cognitive restructuring. Cognitive restructuring begins with discussion of the role of thoughts in generating emotions to provide a treatment rationale. Next, thoughts are recognized as hypotheses rather than fact and therefore open to questioning and challenge. Detailed self-monitoring of emotions and associated cognitions are instituted to identify specific beliefs, appraisals, and assumptions that are

categorized into types of typical errors that occur during heightened emotion, such as overestimations of risk of negative events or catastrophizing of meaning of events. The process of categorization, or labeling of thoughts, is consistent with a personal scientist model and facilitates an objective perspective by which the validity of the thoughts can be evaluated. Thus in labeling the type of cognitive distortion, the patient is encouraged to use an empirical approach to examine the validity of his or her thoughts by considering all of the available evidence. Therapists use Socratic questioning to help patients make guided discoveries and question their anxious thoughts. Next, alternative hypotheses are generated that are more evidence-based. Importantly, cognitive restructuring is not intended as a direct means of minimizing fear, anxiety, or unpleasant symptoms. Instead, cognitive restructuring is intended to correct distorted thinking; eventually fear and anxiety are expected to subside, but their diminution is not the first goal of cognitive therapy.

Exposure. Exposure is a critical phase of treatment and, once begun, is a major focus of treatment sessions as well as homework, since limited exposure practice is of small benefit and may even be detrimental. The exposure is designed to disconfirm misappraisals and extinguish conditioned emotional responses to external situations and contexts through in vivo exposure, as well as to bodily sensations, through interoceptive exposure.

In vivo exposure. In vivo exposure refers to repeated and systematic, real-life exposure, in this case to agoraphobic situations. Most often, in vivo exposure is conducted in a graduated manner, proceeding from the least to the most anxiety-provoking situations on an avoidance hierarchy. However, there is some evidence to suggest that intensive or ungraduated exposure may be effective (e.g., Feigenbaum, 1988).

In vivo exposure typically includes the removal of safety signals and safety behaviors. Examples of safety signals include other people, water, money (to call for help), empty or full medication bottles, exit signs, and familiar landmarks when traveling. Safety behaviors similarly provide a sense of safety and include seeking reassurance or checking for exits. Reliance on safety signals and safety behaviors attenuate distress in the short term but maintain excessive anxiety in the long term. However, recent results contradict the previous findings that safety signals are deleterious for the course of treatment (Rachman, Shafran, Radomsky, & Zysk, 2011) and have found that they do not affect treatment outcome.

Interoceptive exposure. In interoceptive exposure, the goal is to deliberately induce feared physical sensations a sufficient number of times and for long enough each time so that misappraisals about the sensations are disconfirmed and conditioned anxiety responding extinguishes. Interoceptive exposure is now a standard component of CBT for panic disorder (e.g., Barlow, Gorman, Shear, & Woods, 2000; Craske, Lang, Aikins, & Mystkowski, 2005), although different groups give different emphases to interoceptive exposure, with some emphasizing it is a means for extinguishing fear responding (Barlow & Craske, 2006) and others as a vehicle for disconfirming misappraisals (Clark, 1996).

In terms of implementation, a standard list of exercises, such as hyperventilating and spinning, are used to establish a hierarchy of interoceptive exposures. Using a graduated approach, exposure begins with the less distressing physical exercises and continues with the more distressing exercises. It is essential that the patient endure the sensations beyond the point at which they are first noticed, for at least 30 seconds to a minute, because early termination of the task may eliminate the opportunity to learn that the sensations are not harmful and that the anxiety can be tolerated. The coping skills of cognitive restructuring and slow breathing are used after each exercise, followed by a discussion of what was learned during the exercise about bodily sensations, fear, and avoidance. These interoceptive exercises are practiced outside of the therapy session to consolidate the process of learning. Exposure extends to naturalistic activities that inherently induce somatic sensations (e.g., caffeine consumption, exercise).

Medication

Pharmacologic treatment of depression complicated by panic disorder, or panic disorder complicated by depression, is similar to that for either disorder in its uncomplicated form. Selective serotonin reuptake inhibitors (SSRIs) have become the most common first-line treatment for depression with concurrent panic disorder, due to their documented efficacy in both conditions, a favorable side effect profile, and fewer risks of physical complications than previously more common monoamine oxidase inhibitors and tricyclic antidepressants. Many positive placebo-controlled, randomized trials support the efficacy of six different SSRI drugs—fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram, and escitalopram (Roy-Byrne & Cowley, 2002). Placebo-controlled trials (Bradwejn et al., 2005) also support the efficacy for an

extended-release form of venlafaxine in panic disorder. Therapeutic response in panic disorder is a class effect, which is common to all the SSRIs, with no evidence of differential efficacy within the class. Although relevant differences exist in side-effect profiles, drug interactions, and half-life, differences in cost due to availability of the generic forms of these substances (fluoxetine, paroxetine, sertraline, and citalopram are currently available in the United States) are probably much more important.

The older class of tricyclic antidepressants, although associated with more side effects (Bakker, van Balkhom, & Spinhoven, 2002) includes drugs that are both less expensive and similarly effective than newer classes of antidepressants, with many studies indicating efficacy for imipramine, desipramine, clomipramine, nortriptyline, and amitriptyline, (Roy-Byrne & Cowley, 2002) and six older pre-*DSM-III* studies (Roy-Byrne & Cowley, 2002) showing efficacy of monoamine oxidase inhibitors in the phobic anxiety of individuals with panic-like symptoms. These compounds, especially monoamine oxidase inhibitors, can be useful in treatment-refractory patients.

Effect of Comorbid Depression on the Treatment of Panic Disorder

As discussed in the Impact section of this chapter, comorbid major depression slows the natural rate of recovery for panic disorder (Bruce et al., 2005) and has been associated with increased severity of panic disorder and agoraphobia and greater impairment (e.g., Allen et al., 2010; Grunhaus et al., 1994). However, research on how comorbid depression affects the course and outcome of panic disorder treatment has yielded mixed results. Studies focused on CBT for all anxiety disorders and treatment participation have found that comorbidity with depression is associated with increased rates of refusal to enter treatment (Issakidis & Andrews, 2004); however, once patients have entered treatment, the comorbidity has no effect on rates of attrition (Allen et al., 2010; Brown, Antony, & Barlow, 1995).

Preliminary research investigating the effects of comorbidity on engagement with treatment has found that comorbid depression has no effect on compliance with CBT homework (McLean, Woody, Taylor, & Koch, 1998) or compliance with CBT treatment as a whole (Murphy, Michelson, Marchione, Marchione, & Testa, 1998), though it does increase levels of distress associated with treatment (Murphy et al., 1998). There is a need for more research on the ability of depressed patients to engage with the materials presented in treatment, particularly on how comorbidity may affect their capacities to learn the cognitive strategies involved in CBT. As impaired concentration and cognitive functioning is a frequent symptom of depression, future research should investigate how comorbidity may impede learning alternative models of cognitive processing and cognitive interventions for panic disorder.

Research on response rates to CBT has shown that comorbid depression has no effect on the response to treatment at posttreatment or follow-up and in both referred and primary care settings (Allen et al., 2010; McLean et al., 1998; Roy-Byrne et al., 2005). Specifically, a recent large-scale, multisite clinical trial examining long-term treatment strategies for panic disorder among 454 patients (Allen et al., 2010) found that CBT was equally efficacious in the reduction of panic disorder for individuals with and without comorbid depression.

It seems contradictory that comorbid depression would have a significant impact on the severity and persistence of panic disorder but would not affect the outcomes of panic disorder treatment. This may be a product of limitations to the current treatment literature. For example, studies have recruited patients for the treatment of panic disorder and have often excluded patients who are very extremely depressed or suicidal. Thus the majority of patients are mildly to moderately depressed. The results may differ with very extremely depressed patients. Many of these studies also exclude bipolar disorder and therefore exclude an entire group of individuals who experience major depressive episodes.

Effect of CBT for Panic Disorder on Comorbid Depression

Another reason why depression does not affect the treatment of panic disorder is that CBT for panic disorder is also effective in treating symptoms of depression. Baseline levels of depression improve through treatment and thereby confer less of a negative impact on the individual as treatment goes on (LaBerge et al., 1993; Tsao, Mystkowski, Zucker, & Craske, 2002), even when treatment is conducted in a primary care setting (Roy-Byrne et al., 2005). Allen and colleagues (2010) found that symptoms (although not diagnoses) of depressive disorders not addressed in the treatment also showed improvement from pre- to posttreatment. There are several explanations as to why CBT for panic is effective at treating depression symptoms. One is that depression sometimes develops secondary to panic attacks

and other anxiety disorders that are often comorbid with panic. Thus when panic and anxiety symptoms are treated and reduced, secondary depression may subside as well. Another possibility is that the strategies involved in CBT for panic overlap heavily with the strategies used in effective treatments for depression such as cognitive therapy and behavioral activation (Dimidjian et al., 2006; Jacobson, Martell, & Dimidjian, 2001). Last, there may be a down-regulation of processes that are shared by panic disorder and depression that contribute to their initial shared risk and comorbidity, such as changes in levels of neuroticism and perceived control (Craske et al., 2007).

However, despite the positive effects of panic disorder treatment on depression, rates of diagnoses of depression do not decline significantly (Allen et al., 2010; Brown, Antony, & Barlow, 1995). Individuals who do not experience much improvement in panic disorder symptoms and diagnoses after CBT treatment can go on to develop new episodes of major depression over the period between posttreatment and follow-up (Brown, Antony, & Barlow, 1995). The reason for this is unclear but may be related to the severity of their panic disorder diagnosis, the strength of shared risk factors between panic disorder and depression, and/or disappointment in not seeing improvement after treatment.

In sum, CBT is the most heavily researched and evidenced treatment for panic disorder and has shown to be effective in many treatment and research contexts. Treatment involves initial psychoeducation about anxiety disorders and how they affect the physiology of the body, self-monitoring of anxious thoughts and cognitive misappraisals, breathing retraining, cognitive restructuring of distorted thoughts and appraisals, and interoceptive and in vivo exposure to activities and environments on the individual's fear hierarchy. Other forms of treatment include medication, particularly SSRIs. Comorbid depression has mixed effects on the course of CBT for panic disorder, although most recent studies indicate very little effect on patient response to treatment. Furthermore, CBT for panic disorder has positive, yet limited, effects on symptoms of depression. Finally, individuals who receive CBT for panic disorder and do not experience improvement may be at increased risk for future depressive episodes.

Clinical Guidelines for Practitioners

Research investigating the optimal treatment guidelines for comorbid panic disorder and depression is still preliminary, as most treatment studies have focused primarily on effective treatments for either panic disorder or depression, often to the point of excluding comorbid disorders. Thus there is currently no common set of guidelines for treating comorbidity, yet a suggested strategy can be gleaned from the reviewed literature. This strategy starts by determining whether the panic disorder or depression is most severe.

If panic disorder is the principal, or most severely distressing or disabling, diagnosis, the research points to CBT focused primarily on the panic disorder. As reviewed in the previous section, comorbid depression does not appear to affect the outcome of treatment for panic disorder. Clinicians often tailor treatments to accommodate impairments related to depression. A few potential modifications include the addition of pleasant events scheduling, the expansion of cognitive restructuring work to include depressive thoughts, and making sure that the patient does not ignore or downplay his or her own accomplishments in exposure therapy.

However, significant modifications should not be made to the standard CBT for panic disorder as it may impede elements of the treatment that contribute to its effectiveness. Craske and colleagues (2007) compared the effects of a higher dose of CBT for panic disorder versus CBT for panic disorder with additional CBT for comorbid disorders among patients with a principal diagnosis of panic disorder with agoraphobia and other comorbid disorders. They found that patients in the CBT for panic disorder only group saw greater improvement in both their panic disorder and their comorbid conditions at posttreatment and follow-up. The research has also shown mild improvements in depressive symptoms with CBT for panic disorder.

If major depressive disorder is the principal diagnosis, the treatment guidelines are unclear. Studies examining the treatment for panic disorder have typically excluded patients with severe depression and/or have recruited patients with principal anxiety disorders, and there have been no recent studies examining the effects of treatment for depression on comorbid panic disorder. However, it can be assumed that all of the studies of CBT and behavioral therapies for depression have included individuals with comorbid panic disorder and have found these therapies to be effective overall. Thus it may be presumed that if there is a principal diagnosis of depression, treating the depression would also lead to a reduction in panic disorder symptoms.

Summary and Conclusions

In summary, comorbidity between panic disorder and major depression is found in the majority of individuals with panic disorder and a substantial minority of individuals with major depression. Rates of comorbidity between panic attacks and depression are even higher than between full panic disorder and depression. These findings have been consistent throughout epidemiological, clinical, and primary care studies.

Comorbidity between panic disorder and depression has been associated with substantially more severe impacts than either disorder alone, specifically the presence of more and more severe symptoms of each of the disorders, greater persistence of each disorder, more frequent hospitalization and help-seeking behavior, more severe occupational impacts, and a significantly higher rate of suicide attempts.

Not surprisingly, given the high rates of co-occurrence, panic disorder and major depression share many risk factors, most predominantly the personality trait of neuroticism, or the vulnerability to experiencing negative affect, which has been found consistently in both phenotypic and genetic research. Other shared risk factors include exposure to childhood abuse, informational-processing biases, and elevated amygdala activation in response to negative facial expressions.

Research on the development of comorbidity between these two disorders has found that the temporal priority of panic disorder and major depression is mixed and depends largely on the definitions of onset used. Most research has found that panic attacks and other symptoms of anxiety, including other anxiety disorders, typically predate the onset of the first major depressive episode but that the first depressive episode predates the onset of full panic disorder in more than 50% of cases. Developmental research shows that despite high rates of co-occurrence, panic disorder and depression appear to be two distinct disorders as they aggregate separately among families of individuals with both disorders and are associated with different neurobiological substrates.

Finally, the most researched and evidenced-based treatment for panic disorder is CBT. Research has found mixed results on the effect of comorbid depression on the course and outcome of CBT for panic disorder, though most recent research has shown that depression has little effect on treatment response. Additionally, CBT for panic disorder has small but positive effects on comorbid depression.

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CHAPTER

7 Depression and Posttraumatic Stress Disorder Comorbidity

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Abstract

Depression and posttraumatic stress disorder (PTSD) are highly comorbid diagnoses following a traumatic event. In this chapter, we explore a range of topics related to comorbid depression and PTSD, including impact, prevalence, shared risk factors, temporal priority, key research areas, intervention strategies, and future research directions. Given the overlap in symptoms and shared risk factors, some researchers have suggested that the comorbidity between depression and PTSD following a traumatic event may be better understood as a single general mood disorder rather than two separate disorders. We examine evidence supporting both possibilities. We briefly review the two research areas that have received the most attention, namely comorbidity related to military traumas and interpersonal abuse. Practical implications, assessments, interventions, and treatment recommendations are also discussed.

Key Words: posttraumatic stress disorder, PTSD, trauma, depression, comorbidity

Introduction

Introduction to the Specific Comorbidity and Issues

Experiencing a traumatic event is often life-altering and in many cases results in serious mental health problems. Depression and posttraumatic stress disorder (PTSD) are two common mental health problems that co-occur following a traumatic event and result in serious consequences (e.g., suicidal thoughts and actions). In this chapter, we explore a range of topics related to comorbid depression and PTSD, including prevalence, shared risk factors, temporal priority, intervention strategies, and future research directions. Throughout the chapter we use the overarching term "depression" when referring to depressive mood in general, symptoms of depression, or a history of depression and the term "major depressive disorder" (MDD) when referring to the specific *Diagnostic and Statistical Manual of Mental Disorders* (fourth edition [*DSM-IV-TR*]; American Psychiatric Association, 2000) diagnosis.

Definitions of the Disorders and of Comorbidity in this Area

PTSD. PTSD is an anxiety disorder that can develop after exposure to a traumatic event. Traumatic events include experienced events, witnessed events, or events that occur to a close other and may involve the threat of death or physical, sexual, or psychological harm to oneself or another (e.g., rape, combat, natural disasters, life-threatening illness, serious car accident, witnessing a violent death, etc.; American Psychiatric Association, 2000). Approximately 15% to 25% of individuals that experience a trauma develop PTSD (Breslau et al., 1998; Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995). Symptoms of PTSD include reexperiencing the traumatic event through flashbacks or nightmares, avoidance or arousal to stimuli associated with the event, numbing of feelings after the event, and hypervigilance (American Psychiatric Association, 2000). Formal diagnostic criteria per the *DSM-IV-TR* (American Psychiatric

Association,2000) require that the symptoms last more than one month and cause significant impairment in social, occupational, or other important areas of a person's life.

Prevalence. Depression and PTSD are highly comorbid (Kessler et al., 1995). In the United States, the prevalence of MDD among adults is 6.7% annually and 16.6% in a lifetime, and for PTSD it is 3.5% annually and 6.8% in a lifetime (Kessler et al., 2005; Kessler, Chiu, Demler, Merikangas, & Walters, 2005). Twenty-six percent of individuals with PTSD are also diagnosed with current MDD (Maes, Mylle, Delmeire, & Altamura, 2000). Indeed, within eight months of a traumatic event, 23% of exposed adults develop MDD, with or without PTSD, often within days of the event (North et al., 1999).

Preexisting MDD increases risk for both exposure to a traumatic event and to developing PTSD once an individual is exposed to such an event (Breslau, Davis, Peterson, & Schultz, 1997). Additionally, the occurrence of first-time MDD is higher among individuals who develop PTSD following a trauma compared to those that do not develop PTSD following a trauma (Breslau, Davis, Peterson, & Schultz, 2000). Thus the relationship between depression and PTSD is multifaceted; depression appears to increase risk for PTSD and vice versa.

In the National Comorbidity Survey, among men and women with PTSD, lifetime prevalence of comorbid depression was approximately 48% (Kessler et al., 1995). Additionally, in a national sample of adolescents ages 12 to 17, among boys and girls with PTSD, the six-month prevalence of comorbid depression was 62% (Kilpatrick et al., 2003). Similar high rates of comorbidity have been found in both nationally representative samples as well as community samples (Breslau, Davis, Andreski, & Peterson, 1991; Kessler et al., 1995). High comorbidity has also been found among a variety of different samples, including military veteran primary care patients (36% comorbidity; Campbell et al., 2007), urban health care seeking women (58% comorbidity; Gill, Page, Sharps, & Campbell, 2008), and Oklahoma City bombing survivors (55% comorbidity; North et al., 1999).

Impact. A number of studies have compared individuals with comorbid PTSD and depression to those with only one of these disorders. Individuals with both current depression and PTSD suffer more negative mental and physical health consequences than those with either disorder alone (Sher, 2005). For example, compared to depressed patients without PTSD, depressed patients with PTSD have greater psychiatric symptom severity, higher levels of depression and hostility, higher rates of being discharged against medical advice, higher suicidal behaviors, and more medical problems (Calhoun, Wiley, Dennis, & Beckham, 2009; Cougle, Resnick, & Kilpatrick, 2009; Holtzheimer, Russo, Zatzick, Bundy, & Roy-Byrne, 2005; Momartin, Silove, Manicavasagar, & Steel, 2004; Oquendo et al., 2005; Shalev et al., 1998). Additionally, findings from a large-scale epidemiological survey found that individuals with comorbid current depression and PTSD were five times more likely to exhibit functional impairment compared to those with PTSD only (Mollica et al., 1999). These effects have been found across a range of samples, including clinical (Holtzheimer et al., 2005) and community samples (Shalev et al., 1998) and among victims of a range of traumatic events, including motor vehicle accidents (Blanchard, Buckley, Hickling, & Taylor, 1998; Koren, Arnon, & Klein, 1999), war-related trauma (Momartin et al., 2004; Skodol et al., 1996), natural disasters (Tural, Onder, & Aker, 2012), and interpersonal violence (Lipsky, Field, Caetano, & Larkin, 2005).

Biological differences. In addition to the clinical findings noted above, several studies have found biological differences between individuals with comorbid depression and PTSD and those with only one disorder. For example, one study using twin data from the Vietnam Era Twin Registry explored the genetic and environmental components of current depression and PTSD. They found that the, "best-fitting model for the MD–PTSD association included a substantial genetic correlation (r = .77; 95% confidence interval [CI] .50–1.00) and a modest individual-specific environmental correlation (r = .34; 95% CI .19–.48; Koenen et al., 2008, p. 109)." Other biological findings showing differences between comorbid PTSD and depression and either PTSD or depression alone include variations in sleep and facial electromyographic activity (Woodward, Friedman, & Bliwise, 1996), cortisol level (Sher, 2005), and cerebrospinal fluid (Sher et al., 2005). Taken together these studies suggest that there is likely a biological component to the relationship between PTSD and depression.

Risk factors. Given the high comorbidity between depression and PTSD, several shared risk factors have been identified such as a history of prior depression, traumatic event severity, childhood and sexual abuse, and being female (Breslau et al., 1998;

Carlson & Rosser-Hogan, 1991; Kendler, Gardner, & Prescott, 2002; Roberts, Ocaka, Browne, Oyok, & Sondorp, 2008). In addition, Kilpatrick and colleagues (2003) found that among a national sample of adolescents, comorbid current PTSD and depression was more prevalent among females (compared to males), those with a history of familial drug use problems (compared to no history), those who had witnessed violence (compared to those who had not witnessed violence), and those who had experienced sexual and physical assault (compared to no assault).

Shared symptom patterns. In addition to a number of shared risk factors, depression and PTSD also share a number of related symptoms. A subset of PTSD symptoms have been found to be closely related to MDD symptoms, specifically numbing and dysphoria (Gros, Simms, & Acierno, 2010; Simms, Watson, & Doebbeling, 2002). Factor analyses found that these PTSD symptoms (numbing and dysphoria) load more strongly with MDD symptoms than with other specific PTSD symptoms, such as intrusion, avoidance, and arousal (Elhai, Contractor, Palmieri, Forbes, & Richardson, 2010; Gros et al., 2010). Among a large sample of veterans, participants reported the most severe current PTSD symptoms when comorbid MDD and PTSD was present; however, the PTSD only and the major depression only groups consistently reported similar scores on all PTSD symptom measures (Gros, Price, Magruder, & Frueh, 2012). These findings suggest that diagnostic tests for comorbidity may not accurately distinguish between the two disorders.

The similarity in symptoms and risk factors associated with comorbid PTSD and MDD following a traumatic event has led to questions related to whether these disorders should be considered a single mood disorder or if they are truly two distinct disorders. According to Sher (2005), "It is possible that some or all individuals diagnosed with comorbid PTSD and depression suffer from a separate psychobiological condition that can be termed 'post-traumatic mood disorder.' This condition is a result of a trauma, has features of both PTSD and depression, and is more severe than PTSD alone, or depression alone" (p. 208). We address this and other topics related to understanding the development and causal relationship between these two disorders next.

Issues of Development, Temporal Priority, and Cause and Effect

Several possible explanations for the comorbidity of PTSD and depression have been proposed: (a) Depression is a reaction to PTSD, (b) PTSD is a reaction to depression, (c) the two disorders represent a single general traumatic stress factor, and (d) both disorders are separate and distinct reactions to a traumatic event.

Moreover, the classic conceptualization of Meyer (1986) is an excellent overall framework: (a) Disorder X may cause disorder Y; (b) disorder Y causes disorder X; (c) both X and Y are caused by some other factor; (d) each disorder arises independently, with no relation between them; (e) each disorder may impact the course of the other (improving or worsening), even if not caused by it.

These explanations highlight a key question: What does a diagnosis of comorbid PTSD and depression actually mean? We next review the evidence supporting some of these explanations.

There is not a clear temporal order to the comorbidity of depression and PTSD. In fact, the presence of one disorder increases the likelihood of onset of the other. Specifically, individuals with preexisting MDD have twice the risk for exposure to traumatic events and three times the risk of being diagnosed with PTSD following a traumatic event compared to those without a history of MDD (Breslau et al., 1997; Breslau et al., 2000; Bromet, Sonnega, & Kessler, 1998). Similarly, being diagnosed with PTSD increases the risk for developing MDD (including first onset of depression) by nearly three times compared to those exposed to a trauma that do not develop PTSD (Breslau et al., 2000). For example, among survivors of the Oklahoma City bombing, 55% of individuals with current PTSD developed MDD whereas fewer than 9% of trauma survivors without PTSD had MDD (North et al., 1999). In sum, such findings indicate that PTSD is a risk factor for MDD and vice versa—a history of MDD increases the risk for PTSD.

A number of studies support the idea that comorbidity of PTSD and depression following a traumatic event represents a single general traumatic stress factor (sometimes referred to as posttraumatic mood disorder; see Sher, 2005). One study found that among accident survivors from intensive care units (mostly motor vehicle accidents), the majority of survivors diagnosed with PTSD and depression did not differ from PTSD-only survivors in terms of variables that differentiated them from a group without PTSD. Specifically, at 3 and 12 months the same combination of variables was able to differentiate the PTSD-only group from the no-PTSD group, and the comorbid-PTSD and depression group from the no-PTSD group. Variables included event

characteristics (intensive care unit admission, event severity), individual characteristics (prior psychiatric and trauma history), cognitive appraisals (anxiety about the potential impact of the injury), and acute responses (reexperiencing, arousal, and depression). Different predictors did emerge between the depression-only group and the comorbid group, suggesting that depression may exist as a separate disorder in some cases. The authors conclude:

> It is clear that the bulk of psychopathology in the aftermath of trauma is best conceptualized as a general traumatic stress factor . . . it would seem that the PTSD and depression symptoms that constitute this factor are part of a shared vulnerability and thus have the same predictive variables. PTSD and comorbid PTSD/depression are effectively one and the same thing. The data suggest that depressive symptoms are often integral to PTSD and that to separate depression out as a distinct disorder when it occurs with PTSD is a somewhat arbitrary distinction. (O'Donnell, Creamer, & Pattison, 2004, p. 1395)

These findings reinforce conclusions from the earlier studies we reviewed (e.g., Breslau et al., 1997; Breslau et al., 2000; O'Donnell et al., 2004) that comorbid PTSD and depression in the aftermath of trauma may best be conceptualized as a single traumatic stress construct with shared risk factors and symptoms.

The final explanation for the comorbidity between PTSD and depression is that the disorders are separate constructs. Supporting this position, several studies indicate variations among different outcomes related to PTSD or depression only and comorbid PTSD and depression. For example, a study of victims of motor-vehicle accidents found that PTSD and MDD were correlated, but independent, diagnoses following the trauma (Blanchard et al., 1998).

A recent study (Chiu et al., 2011) examined risk factors associated with comorbid depression and PTSD in an attempt to elucidate whether depression and PTSD represent separate constructs or a single general stress reaction to a traumatic event. Using a sample of retired World Trade Center firefighters, they found that the relationship between current PTSD and alcohol abuse was mediated by depression. Similarly, World Trade Center arrival time was associated with current depression, but this association was mediated by PTSD. The authors conclude, "Our models suggest that elevated depression and PTSD risk may be separate constructs. After controlling for comorbidity in the current study, we identified unique correlates for each condition, which support the premise that depression and PTSD are independent responses to trauma" (Chiu et al., 2011, p. 207).

In sum, there exists a complex relationship between depression and PTSD. All four explanations for this comorbidity have received research support. More research is needed to continue to explore this intricate relationship and to determine whether diagnoses of depression and PTSD following a traumatic event are separate constructs or one disorder.

Types of Trauma

The majority of research on comorbidity of PTSD and depression generally falls into two categories of trauma types: (a) veterans/military-related trauma and (b) interpersonal violence/sexual assault. We briefly review these two areas of research.

Veterans/Military-Related Trauma

Research on military veterans has consistently demonstrated a high prevalence of comorbid PTSD and depression. Moreover, this comorbidity makes veterans vulnerable to other significant problems such as suicidal ideation and behavior (Lemaire & Graham, 2010; Oquendo et al., 2005). Long-term impact of traumatic events on comorbid PTSD and depression has also been found, such as in a study of Korean War veterans conducted 50 years after the war. Findings indicated that a notable minority (17%) of veterans had comorbid current PTSD and depression and that this comorbidity was associated with impaired life satisfaction, reduced quality of life, and greater symptom severity (Ikin, Creamer, Sim, & McKenzie, 2010).

Some research has examined gender differences among veterans. For example, a recent study (Maguen, Cohen, Cohen, et al., 2012) examined health care utilization among male and female Operation Enduring Freedom/Operation Iraqi Freedom veterans with current PTSD. Findings indicate that males and females with comorbid PTSD and depression were more likely to have higher mental health, primary care, and emergency care use compared to the PTSD-only group. Notable gender differences emerged such that "women with comorbid PTSD and depression were 12.5 times more likely to have a mental health inpatient hospitalization compared to their female counterparts without depression and twice as likely to have a mental health hospitalization compared to men with comorbid PTSD and depression (p. 666)."

Veterans from Operation Enduring Freedom/Operation Iraqi Freedom who had higher combat exposure, childhood physical assault, and accident/disasters were significantly more likely to have current PTSD and MDD compared to veterans without these trauma experiences (Dedert et al., 2009). Among veterans from primary care settings, patients with current comorbid PTSD and depression report more severe depression, lower social support, more outpatient health care visits, more suicidal ideation, more emotional distress, more frequent mental health specialty visits, and correspondingly higher outpatient mental health care costs compared to depression-only patients (Campbell et al., 2007; Chan, Cheadle, Reiber, Unutzer, & Chaney, 2009). Additionally, antidepressants were prescribed to a higher proportion of depressed patients with PTSD compared to depression-only patients (61% vs .40%; Chan et al., 2009).

Veterans are at high risk for both PTSD and depression, and these have known negative sequelae. However, more research is needed to understand the many factors that may account for these findings. Veterans may experience trauma prior to their military service; thus, it is necessary to disentangle the impact of trauma prior to their military career as well as postdeployment experiences that impact their mental health.

Interpersonal Violence

The comorbidity of depression and PTSD has been found to be consistently high among victims of rape or physical abuse. Approximately 50% of interpersonal violence victims report comorbid depression and PTSD (Nixon, Resick, & Nishith, 2004; Stein & Kennedy, 2001). Among a sample of Rwandan women with HIV, high levels of comorbidity were found such that 82% of women with PTSD also had depression, and of the women with depression, 63% also had PTSD (Cohen et al., 2009).

Compared to only one disorder, risk factors for comorbid PTSD and depression among victims of interpersonal or sexual violence include suffering an adult rape or military sexual trauma, greater psychological abuse, and higher rates/more severe symptoms of PTSD and depression (Lipsky et al., 2005; Maguen, Cohen, Ren, et al., 2012; Nixon et al., 2004). Similarly, in a sample of adolescents a history of sexual abuse was related to a higher prevalence of comorbid PTSD and depression than adolescents without such a history. The frequency and severity of the abuse increased the likelihood of the comorbidity (Brand, King, Olson, Ghaziuddin, & Naylor, 1996).

In addition, men with a history of childhood sexual abuse and current comorbid PTSD and depression are more likely to engage in risky sexual behavior compared to men without an abuse history (Holmes, Foa, & Sammel, 2005). Also, compared to men without a history of child abuse, men that experienced child abuse were found to be three times more likely to report high PTSD and depression symptoms among disaster workers following the terrorist attacks on September 11, 2011 (Leck, Difede, Patt, Giosan, & Szkodny, 2006).

Women who are victims of interpersonal and/or sexual trauma are also at an increased risk for comorbid PTSD and depression. One key component to developing appropriate treatments and interventions is to gain a better understanding of various coping trajectories that women with this comorbidity tend to use (Arriaga & Capezza, 2005). While the research on adult interpersonal violence described above focuses on women, men are also victims of interpersonal violence and suffer negative consequences, including depression and PTSD (Coker, Weston, Creson, Justice, & Blakeney, 2005). However, we were unable to locate any studies examining comorbid depression and PTSD among adult males who are victims of interpersonal violence. Certainly this is an important topic deserving future research attention.

Assessment and Intervention Strategies

Assessment

Several considerations are relevant to assessment of comorbid PTSD and depression. As detailed earlier, individuals with this comorbidity are likely to have additional co-occurring Axis I and Axis II disorders. Thus assessment needs to address the full array of clinical presentations. It can be helpful to use a brief *DSM-IV* structured interview, such as the MINI Neuropsychiatric Interview (Sheehan et al., 1997) or the Structured Clinical Interview for *DSM-IV* (First, Spitzer, Gibbon, & Williams, 1997a; First, Spitzer, Gibbon, & Williams, 1997b). By assessing the wide range of psychiatric conditions, a profile of comorbidity, in its most complete sense, can help inform treatment planning.

Also, there may be many clinically relevant areas to assess other than just diagnoses. For example, clinical issues that may be prominent in comorbid PTSD and depression may include employment problems, family and social problems, motivational

problems, and physical health problems (Evans & Hser, 2004).

Another key consideration (per earlier in this chapter) is the significant overlap between PTSD and depression symptoms. Disentangling which symptoms relate to each disorder and which are genuinely part of both is a challenge. Sometimes a life trajectory approach can be helpful (identifying which disorder arose first and which symptoms occurred in relation to onset of the disorders). However, for clinical purposes, the bottom line may simply be that the patient currently meets criteria for both PTSD and depression and would thus need clinical attention for both.

It is essential to use validated instruments. The most basic are screening tools that are brief, typically self-report, and identify the likelihood that the individual may have the disorder. In many settings, such as primary care, substance abuse treatment programs, and front-line community agencies, there may only be time for screening instruments, given time and staff limitations. For depression, the Patient Health Questionnaire-9 (Kroenke, Spitzer, & Williams, 2001) is one of the most common currently used screening instruments. The Beck Depression Inventory-2 (Beck, Steer, & Brown, 1996) is also widely used. It takes longer but provides cutoffs for different levels of depression and can be used as an outcome measure as well as a screening tool. For PTSD, the four-item screen designed for primary care is also widely used in a variety of settings (Prins et al., 2003). The PTSD Checklist (Weathers, Litz, Herman, Huska, & Keane, 1993) is longer but offers the advantage of mapping onto *DSM-IV* criteria for PTSD and offering the option to have a continuous measure for outcome purposes. For PTSD, it is also essential to obtain a screen for trauma itself, for which there are various screening tools, such as the Life Events Checklist (Gray, Litz, Hsu, & Lombardo, 2004) and the Stressful Life Events Screening Questionnaire (Goodman, 1998). If a patient screens positive on the screening tool (for depression, PTSD, or both), a trained assessor can then conduct a full diagnostic assessment using *DSM-IV* criteria (e.g., the MINI Neuropsychiatric Interview or the Structured Clinical Interview for *DSM-IV*, for example, per above). Following assessment, it would be important to obtain outcome measurement if the patient is entered into treatment. Measures for outcome assessment are plentiful. For depression, in addition to the Beck Depression Inventory already noted, there are the Hamilton Depression Scale (Hamilton, 1967), the Center for Epidemiological Studies Depression Scale (Radloff, 1977), and the Zung Self-Rating Depression Scale (Zung, 1965). For PTSD, in addition to the PTSD Checklist, there are the Trauma Symptom Inventory (Briere, 1995), which obtains a broad range of trauma-related symptoms, and the Modified PTSD Symptom Scale (Falsetti, Resnick, Resick, & Kilpatrick, 1993), which obtains frequency and severity ratings for each of the 17 *DSM-IV* PTSD criteria (and can be used for outcome assessment).

Intervention

Several general points related to treatment of comorbidity are notable before we explore specific findings on PTSD–depression comorbidity.

First, an overall framework on comorbidity treatment can be helpful. Treatments can be categorized into the following approaches (for expanded version see; Najavits et al., 2008; Weiss & Najavits, 1997).

– *Integrated– continuous:* Designed to treat both disorders at the same time, by the same provider, focusing on linkages between them throughout.

– *Integrated– phase based:* Focuses primarily on one disorder, then the other, by the same provider and with some attention to both disorders throughout.

– *Sequential*: Treats one disorder, then the other (may be by different providers and may be based on response to the initial treatment, such that the patient improves in one disorder and then addresses the other).

– *Parallel*: Also known as concurrent (i.e., treat each disorder but in separate treatments), often by different providers.

– *Single*: Treat just one disorder.

Second, even treatments designed for PTSD or depression alone may have an impact on the other disorder—even if not designed specifically to treat it; many treatments have generalized impact beyond their targeted disorder (Najavits et al., 2008; Watts, 2007).

Third, in PTSD treatment trials, a sizeable percentage of patients inevitably also had comorbid depression, even if it was not assessed, given what we have reviewed above on substantial comorbidity of PTSD and depression. The same holds for depression studies in terms of inclusion of PTSD patients.

At this point, we know of only one behavioral therapy model specifically designed a priori

to address PTSD–depression comorbidity. (For information on pharmcotherapies, see Friedman, 2002; Sher et al., 2012; Stewart & Wrobel, 2009). The behavioral model is described by Nixon and Nearmy (2011) and represents a combination of already existing cognitive behavioral treatment components that have received evidence-based support for depression or PTSD separately: behavioral activation for depression in early sessions, followed by exposure therapy and cognitive restructuring for PTSD in later sessions, for a total of 12 to 16 weeks per patient. This approach fits the "integrated phase based" category described above. They found, in a sample of 14 patients who completed treatment, a significant decrease in PTSD and depression severity between pre- and midtreatment assessments and a further decrease in PTSD from mid- to posttreatment. Gains were maintained at three-month follow-up; 60% of the sample no longer met PTSD criteria and 70% no longer met MDD criteria at that point. This treatment package is thus a highly promising one for future research.

Another example of a treatment trial relevant to PTSD–depression comorbidity is that of Dunn et al. (2007). They evaluated the impact of an evidence-based depression treatment (self-management therapy) on patients with depression and chronic PTSD. Specifically, they randomized 101 male veterans with chronic combat-related PTSD and depressive disorder to the self-management therapy condition versus an active-control therapy. Their primary outcomes, using an intent-to-treat design, were subjective and objective PTSD and depression scales at pretest, posttest, and 3-, 6-, and 12-month follow-up. Secondary outcomes included treatment compliance, satisfaction, treatment-targeted constructs, functioning, service utilization, and costs. They found that self-management therapy had modestly greater improvement on depression symptoms at treatment completion, but these were not maintained at follow-up. They also found that psychiatric outpatient utilization and overall outpatient costs were lower with self-management therapy. They concluded that "Despite success in other depressed populations, self-management therapy produced no clinically significant effect in depression with chronic PTSD" (p. 221). However, future research could potentially evaluate the impact of the treatment in other PTSD–depression populations, as results for male veterans with chronic combat-related PTSD may not generalize to other populations.

Overall, there is a striking dearth of treatments and treatment outcome trials on PTSD–depression comorbidity, considering the large number of patients affected, and its notable impact. However, the decades ahead are likely to see new developments in these areas, given the increasingly prominent focus on comorbities of all kinds and the greater prominence of PTSD-related research specifically.

Practical Issues and Clinical Guidelines for Practitioners

Several practical suggestions can be offered that may help inform care, drawn from earlier work on comorbidity treatment (e.g., Najavits et al., 1997; Najavits, Ryngala et al., 2008; Weiss & Najavits, 1997).

(a) When patients present with comorbid PTSD and depression (or any other comorbidities), they should be given care that addresses all current disorders.

(b) Treatment of comorbid disorders is generally more complex than treatment of either disorder alone. The clinician needs to monitor symptoms of both disorders and how they interact over time. Also, the clinician should provide psychoeducation so that the patient can recognize and chart symptoms of each disorder.

(c) Patients may be more motivated to work on one disorder than the other and may need encouragement to attend to both for as complete a recovery as possible.

(d) The clinician too may feel more connection or engagement with one disorder over the other and thus may lack balanced attention to the comorbidity. For example, PTSD may evoke more sympathy as it is so clearly connected to an external event (the trauma); or, alternatively, PTSD may be more likely to be ignored as historically, at least, it typically has been relative to depression (Najavits et al., 2008).

(e) Both depression and PTSD are highly associated with additional comorbid disorders that have major clinical impact, such as substance use disorders and Axis II disorders. The treatment course and strategies may need to be altered when such additional comorbidities are present.

(f) Depression or PTSD subtypes may also impact the course and treatment of the disorders, such as depression with or without psychotic features, early or delayed PTSD, and so on.

(g) The clinician should recognize that there may be various subpopulations with elevated rates

of PTSD and depression, including women, the homeless, adolescents, veterans, and individuals who are incarcerated. These patient groups may need different approaches to care or adapted treatments relevant to their needs.

(h) The clinician should provide referrals to additional treatments and conduct a thorough assessment of case management needs. Patients with depression and PTSD may need treatment of physical health problems, medication consultation, couples or family treatment, parenting skills, and so on. Each of the disorders can additively impact their functioning, and, in general, the more treatment and the more varied the treatment, the better.

Also, see Campbell et al. (2007) for an excellent guide to PTSD–depression comorbidity in relation to primary care in particular but that also has relevance more broadly. They observe that this comorbidity is common, yet many patients are treated solely for depression. Moreover, patients with the comorbidity, compared to those with depression alone, have a more severe clinical profile, including poorer prognosis, delayed response to depression treatment, higher likelihood of being disabled, a more persistent course of illness, increased prevalence of suicidal ideation, and less social support. In short, they have an increased illness burden that likely requires different treatment strategies than depressed-only patients. They state, "In summary, depressed patients with positive PTSD screens present differently from those with depression alone. Relative to what is known about effective primary care–based depression treatment (Belnap et al., 2006; Kilbourne, Rollman, Schulberg, & Pincus, 2002) less is known about primary care treatment of PTSD and MDD-PTSD comorbidity" (p. 716). They emphasize the need for further treatment outcome research on this population.

Finally, one study found empirically that patients with PTSD and depression, compared to depressed patients without PTSD, had higher costs of treatment. They used specialty mental health treatments and antidepressant medications more and had overall higher mental health care costs. Similarly, Fikretoglu et al. (2009) found that most military members with PTSD did not seek out mental health treatment but that, of all the predictors, comorbid depression most increased the likelihood of seeking treatment. Overall, these studies suggest increased treatment seeking (and associated costs) among people with PTSD and depression. These studies, however, were in veteran and military populations, respectively, and so more research is needed before generalizing to other populations.

Future Directions for Research and Clinical Practice

1. There is a need for practice guidelines that address the comorbidity of PTSD and depression. Such guidelines might address key clinical issues such as how to address both disorders at the same time and how to monitor patients for potential harm to self or others (which may be increased due to each disorder and their comorbidity).

2. Future research and clinical practice should address additional comorbidities that commonly co-occur with PTSD and depression, such as substance use disorders and Axis II disorders, which can have major impacts on clinical presentation.

3. Future treatment outcome research on PTSD or depression treatments should include rates of comorbid disorders, even if the treatments are not designed to address comorbidity. Treatments often have impact beyond the targeted disorder, and such information could be valuable for identification of treatment pathways.

4. Patients with PTSD and depression come through many different treatment "doors"—that is, systems of care, including primary care, specialty care, correctional settings, schools, and veterans hospitals. It will be important to address how treatment may differ depending on setting-based issues such as provider training and workload issues, culture of the setting, costs, and so on. For example, in primary care, the focus may be primarily on brief education and referral to specialty care. In specialty care, the focus would be more intensive, such as multimodal approaches (e.g., medications plus behavioral therapies) as well as long-term management of the disorders.

5. There is a need for more widespread screening and assessment of both PTSD and depression. Including brief self-report screening tools for each disorder as part of the intake process may help promote early case-identification and treatment.

6. More research is needed on the etiology and presentation of comorbid PTSD and depression, including order of onset of the disorders, social and biological pathways, and subtypes of the disorders. All of these may impact treatment response as well as are important for scientific advancement.

7. Various subpopulations (e.g., women, veterans, military, victims of child abuse) have particularly high rates of PTSD–depression comorbidity, and there may be a need for specialized or targeted treatments for them. For example, children and adolescents likely need treatments that take into account their developmental concerns and use language, examples, and exercises relevant to them.

8. More research examining comorbid PTSD and depression among male victims of interpersonal violence is needed.

9. Additional research is needed on the impact of comorbidity following less-studied traumatic experiences, such as life-threatening illness, witnessing a violent death, and so on.

10. There is a definite need for more treatment development and treatment outcome trials focused on PTSD–depression comorbidity, particularly considering the large number of patients affected by the comorbidity and its notable impact.

Summary and Conclusions

Comorbid depression and PTSD is highly prevalent and results in many negative consequences. The two disorders have similar impact, share risk factors, and share symptoms. Given the similarities between the two disorders, researchers have questioned whether the diagnoses of PTSD and depression following a traumatic event are actually two separate disorders or one general mood disorder. Understanding this distinction may help in developing relevant intervention and treatment efforts for this comorbidity. The majority of research on PTSD and depression comorbidity has focused on traumas related to military experience and interpersonal violence victimization. It is unclear whether these findings would generalize to other traumatic experiences.

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CHAPTER

8

Comorbidity of Social Anxiety Disorder and Depression

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Abstract

Social anxiety disorder (SAD) and major depressive disorder (MDD) are prevalent disorders that exhibit a high rate of co-occurrence. Furthermore, these disorders have been shown to be associated with each other, suggesting that the presence of one disorder increases risk for the other disorder. In this chapter, we discuss relevant theories that attempt to explain why SAD and MDD are related. We propose that the available evidence provides support for conceptualizing the comorbidity of SAD and MDD as resulting from a shared underlying vulnerability. There is evidence that this underlying vulnerability is genetic in nature and related to trait-like constructs such as positive and negative affect. We also discuss the possibility that the underlying vulnerability may confer tendencies toward certain patterns of thinking. Finally, we discuss theories that propose additional causal pathways between the disorders such as direct pathways from one disorder to the other. We advocate for a psychoevolutionary conceptualization that links the findings on the underlying cognitions to the shared relation of lower positive affect and the findings on peer victimization. We suggest that, in addition to a shared underlying vulnerability, the symptoms of social anxiety and depression may function as a part of a behavior trap in which attempts to cope with perceived social exclusion lead to even higher levels of social anxiety and depression. Finally, we make recommendations for the best methods for assessing SAD and MDD as well as suggestions for treating individuals with both disorders.

Key Words: social anxiety disorder, major depressive disorder, depression, comorbidity, conceptualizing the comorbidity

Introduction

Social anxiety disorder (SAD) and major depressive disorder (MDD) are common psychological disorders, with lifetime prevalence rates estimated to be 12.1% and 16.6%, respectively (Kessler, Berglund, et al., 2005). The high rate of comorbidity between these two disorders has been well documented (Beesdo et al., 2007; Brown, Campbell, Lehman, Grisham, & Mancill, 2001; Kessler, Chiu, Demler, & Walters, 2005; Ohayon & Schatzberg, 2010; Stein et al., 2001), and, of the anxiety disorders, SAD exhibits one of the highest degrees of association with MDD (Kessler, Chiu, et al., 2005). Despite a large body of research on the rate of comorbidity between these disorders and various theories or models that attempt to explain why these disorders are related, many of the available theories are either difficult to falsify or not strongly supported by the data that are currently available. We discuss a conceptualization that we believe is most consistent with the available data as well as propose additional explanatory factors that we find plausible but require further testing. First, we make the case that the specific relationship of SAD to MDD is important to consider. Second, we discuss the best methods for measuring comorbidity. Third, we discuss the conceptualization of SAD and MDD that we find most consistent with the

data. Fourth, we review research that is consistent with this conceptualization, and, finally, we discuss potential additions to this conceptualization that we find plausible. We also discuss the best methods for assessing social anxiety and depression as well as outline strategies for treating individuals who present with both disorders.

Comorbidity Between SAD and MDD: More than the Sum of its Parts

Why is it important to consider the comorbidity between social anxiety and depression? It seems to us that comorbidity might be reasonably ignored if having two disorders in one person was equivalent, in terms of burden or distress, to having one disorder each in two people. We believe that research has established reasonably clearly, however, that having both disorders together actually creates more distress and burden.

Essentially, the comorbidity of SAD and MDD is associated with impairment beyond merely having one of the disorders. For example, Bruce et al. (2005) reported that the addition of MDD to SAD worsens the already low level of recovery associated with SAD. Furthermore, researchers have reported that individuals with both SAD and MDD are more likely to have additional anxiety disorders, see a psychiatrist, take psychotropic medications, have more intense suicidal ideation, experience more depressive symptoms, and have a longer duration of major depressive episodes (Ohayon & Schatzberg, 2010; Stein et al., 2001) than individuals with either SAD or MDD. Additionally, Stein et al. reported that individuals with both disorders (vs. only one) also had much greater odds of having attempted suicide during a follow-up period. Indeed, previous research indicates that depression, social anxiety, and their interaction each predict unique variance in suicidal ideation, indicating that there are both additive and interactive effects of social anxiety and depression on suicidal ideation (Norton, Temple, & Pettit, 2008).

We find the final point mentioned above most compelling, because an interaction between the two disorders in predicting suicidal ideation provides clear evidence that comorbidity between SAD and MDD is not merely the sum of its parts. The presence of such interactive effects is a vital reason to take comorbidity into account in both research and treatment. In this section, we have argued for the importance of comorbidity without giving an operational definition for it. Given that our ability to consider comorbidity in research will be influenced by our method for assessing comorbidity, we now turn to a discussion of the best method for measuring the degree of overlap and association between these disorders.

Rates of Comorbidity

In terms of the best method for capturing the degree of association between SAD and MDD, we find the Kessler, Chiu, et al. (2005) comorbidity study to be one of the most useful because the authors report correlation results rather than merely the rate of overlap between the disorders. As noted by Krueger and Markon (2006), the term *comorbidity* does not distinguish between correlation and overlap. The correlation between two disorders captures the extent to which the disorders co-occur at higher rates than would be expected by chance within a population. In contrast, a high degree of overlap might simply represent chance (or even *below chance*) co-occurrence of two common disorders. Although mere co-occurrence may be of interest (e.g., two disorders need not be associated to have compounding effects), we find correlations (or associated methods, such as odds ratios) more compelling than mere co-occurrence. We expect that most researchers and clinicians are, similarly, interested in comorbidity because it indicates possible correlation, not mere co-occurrence.

It is thus of considerable interest that Kessler, Chiu, et al. (2005) report a significant and moderate tetrachoric correlation between a diagnosis of SAD within a 12-month period and a diagnosis of MDD within a 12-month period ($r = .52$), which, in their analysis, is the second highest association with MDD among the anxiety disorders. Such an association implies that there is something specific about one of these disorders itself that increases the odds of having the other during the same time period, above and beyond more general factors (e.g., SAD being an anxiety disorder or internalizing disorder).

Note that any method of assessing comorbidity, either in terms of association or overlap, must make use of a specific timeframe. Disorders can be assessed in terms of lifetime prevalence, onset of disorder during specific time frames (measured longitudinally), or current diagnoses, which raises the question of which method is of most importance in understanding comorbidity. Although lifetime prevalence rates may be useful for some purposes, the documented limitations of retrospective reporting (e.g., Henry, Moffitt, Caspi, Langley, & Silva, 1994) lead to questionable accuracy of cross-sectional lifetime prevalence estimates. Measuring current diagnoses or following participants over time have greater claims

to potential accuracy and precision. Longitudinal data are particularly important because they not only side-step the issue of retrospective reporting but also allow researchers to test the ability of one disorder to prospectively predict another. For example, Beesdo et al. (2007) assessed participants four times over a 10-year period and found that 50.2% of respondents with SAD also had a depressive disorder at some point during the observation period. We believe it is obvious that longitudinal data are preferable, but they are often not obtainable, and many findings regarding MDD and SAD focus on retrospective lifetime prevalence or current diagnosis. For example, Ohayon and Schatzberg (2010) reported that 19.5% of those with current SAD also met criteria for current MDD.

We have thus far referred to MDD, but the comorbidity between SAD and depression is often studied in broader terms. Some studies consider diagnoses of only MDD as *depression* (e.g., Ohayon & Schatzberg, 2010), whereas others include MDD with other mood disorders such as dysthymia (e.g., Van Ameringen, Mancini, Styan, & Donison, 1991). MDD is characterized by depressed mood or loss of interest more days than not for at least two weeks, whereas dysthymia is a form of depression in which the individual is not without the depressed mood for more than two months over at least a two-year period (American Psychiatric Association, 2000). We find it plausible that both MDD and unipolar depressed mood more broadly may have important relationships with SAD.

In regard to future research and the conceptualization of depression, we recommend measuring both dysthymia and MDD but reporting the results with the disorders considered separately as well as combined to assess how these two methods influence the findings. If more studies currently in the literature had followed this recommendation, we could have included in our review the question as to what impact including dysthymia in comorbidity for SAD would have. Absent a critical mass of literature in this regard, we have focused on being clear regarding the existing literature: We use the term *MDD* when a study restricted the sample to only those with this diagnosis, but we use the word *depression* to discuss the general condition of low mood.

Theories Regarding SAD and Depression Comorbidity

Given the substantial overlap in occurrence between SAD and MDD (e.g., Gibb, Coles, & Heimberg, 2005), researchers have sought to determine what accounts for this high degree of overlap. Three basic theories regarding this overlap have either been articulated or implied by the available literature: (a) SAD and MDD co-occur because of a shared underlying vulnerability that fully accounts for the high rate of comorbidity; (b) in addition to a shared underlying vulnerability, additional causal pathways exist between the two disorders; and (c) there are intervening variables that arise from one disorder that confer risk for the other disorder. Prior to reviewing these theories in detail, it seems prudent to give an overall sense of their current support. Available data support statement (a) and can be seen as consistent with (b) or (c), but a test of whether SAD and MDD continue to be associated above and beyond any specific shared vulnerability (e.g., genetic predispositions) has yet to be completed.

Speaking strictly to the available data, we believe that the best conceptualization of the relationship between SAD and MDD is that these disorders are related because of a shared vulnerability conferred by low positive and high negative affect. Much of this shared vulnerability may be genetic in origin, yet our primary assertion is that whatever leads individuals to have lower positive and higher negative affect on a chronic basis will tend to confer risk for both disorders. We review the evidence for this proposition below, primarily in regard to positive affect because negative affect appears to be a risk factor for emotional disorders in general.

Available data can also be found that are consistent with the hypothesis that SAD, or the consequences of SAD, confer additional risk for MDD, above and beyond the shared vulnerability. For example, given that both disorders are related to lower positive affect, it has been suggested that a causal pathway exists between SAD, lower positive affect, and MDD. At present, no single study tests the plausibility of a causal pathway from SAD to MDD longitudinally while simultaneously accounting for shared vulnerability (e.g., premorbid lower positive affect). Absent such tests, we review the data that is consistent with additional causal pathways primarily to suggest what further testing is needed.

In the next sections, we examine the shared vulnerability and specific causal pathways theories and evidence in more detail. First, we review research that supports a shared underlying genetic vulnerability as well as research that is often cited as support for a direct association but can also be explained by

a shared vulnerability. Second, we propose a characterization of the shared underlying vulnerability. Third, we discuss propositions of additional causal pathways that seem plausible but require direct testing. Fourth, we discuss research on treatment response in the context of the shared vulnerability versus specific causal pathways theories. Finally, we discuss recommendations for assessment and intervention for SAD and MDD.

Evidence for Shared Underlying Vulnerability Versus Specific Causal Pathways

Heritability

Previous research supports a genetic influence for both SAD and MDD (Fyer, Mannuzza, Chapman, Liebowitz, & Klein, 1993; Kendler et al., 2011; Ogliari et al., 2006). Additionally, twin studies suggest a genetic association between SAD and MDD (Kendler, Neale, Kessler, Heath, & Eaves, 1993; Merikangas & Angst, 1995), and relatives of people with SAD have been found to have an increased risk of MDD even after controlling for the risk of depression in the person with SAD (Fyer et al., 1993). These findings suggest that the comorbidity between SAD and MDD is at least partly explained by shared genetic risk. Kendler et al. (1993) reported that 48% of the observed comorbidity between SAD and MDD was explained by shared genetic factors, whereas 52% was due to unique environmental factors that were shared by both disorders. This finding suggests that although shared genetics likely explains part of the high rate of comorbidity between SAD and MDD, other shared vulnerabilities are present such as common environmental influences that are unique to an individual (not shared within families).

Kendler, Heath, Martin, and Eaves (1986) provide additional evidence supporting a shared genetic risk for both anxiety and depression as well as specific environmental contributions. The authors found support for a general genetic risk for both anxiety and depression symptoms and a more specific risk conferred by nonshared environmental influences. The authors also found support for an independent pathway model in which genes had direct pathways to symptoms, rather than a pathway extending from genes, to a disorder, and then to the symptoms. This finding suggests that any existing genetic risk does not confer risk for a specific syndrome; rather, the risk is directly related to symptoms, including both anxiety and depression symptomatology. Although we expect these results are applicable to the question of SAD and depression comorbidity, this conclusion would be clearer if the study were replicated with social anxiety symptoms rather than general anxiety symptoms.

Given the substantial relationship between extraversion and neuroticism and the mood and anxiety disorders (Clark, Watson, & Mineka, 1994), researchers have investigated the genetic relationship between these personality traits and various psychological disorders. Bienvenu, Hettema, Neale, Prescott, and Kendler (2007) reported that the genetic contribution to extraversion and neuroticism completely accounted for the genetic risk for SAD. These personality traits have a strong genetic component (Jang, Livesley, & Vernon, 1996), suggesting that they may mediate the relationship between genetic makeup and SAD. The authors did not find evidence for a shared environmental liability or genetic risk specific to SAD (over and above that related to extraversion and neuroticism).

Findings on the genetic risk for both SAD and MDD support a theory that allows for shared underlying genetic and environmental vulnerabilities for both disorders. However, there may be additional unique genetic risks for each disorder as well as unique environmental contributions. The findings of Bienvenu et al. (2007) suggest that any such genetic risk affects trait-like affective variables, such as neuroticism, extraversion, or positive and negative affect, more directly than symptoms of specific disorders.

Associated Risk Between the Disorders

Abundant evidence that SAD and depression occur together, as well as evidence that depression often follows SAD (Beesdo et al., 2007; Brown et al., 2001) could be cited as evidence that there is a direct causal relationship between the two disorders. However, the data available do not make clear that any such apparent causal relationship maintains above and beyond an underlying vulnerability. Thus, although existing studies are certainly consistent with the notion that one disorder (primarily SAD) specifically leads to the other, the same studies do not rule out the possibility that a shared underlying vulnerability serves as a more parsimonious explanation of the data.

For example, Stein et al. (2001) reported that participants ages 18 to 24 who qualified for SAD at baseline but did not meet criteria for depression (current or previous) were significantly more likely than participants with no mental disorder to meet criteria for a depressive disorder during the

follow-up period. For participants who met criteria for a depressive disorder at baseline, an additional diagnosis of SAD (either current or previous) at baseline approximately doubled the odds of developing subsequent depression or depression that persisted to the follow-up period. However, given a shared vulnerability of some type between SAD and MDD, it would be inevitable that people in the population with the greatest levels of vulnerability should be more likely to have at least one of the disorders at any given time. The development of the other disorder at another time point might therefore depend merely on the level of the vulnerability rather than a specific pathway from one disorder to another.

Temporal Relationship

The tendency for SAD to predate the onset of MDD in individuals with both disorders has been well documented in the literature (Brown et al., 2001; deGraaf, Bijl, Spijker, Beekman, & Vollebergh, 2003) and could be interpreted as evidence for a direct causal pathway. SAD in general tends to begin at an early age (e.g., Dalrymple & Zimmerman, 2011; deGraaf et al., 2003; Kessler, Berglund, et al., 2005), especially for the generalized (nonspecific) subtype (Wittchen, Stein, & Kessler, 1999). Most reports of the typical age of onset of SAD range from childhood to the middle adolescent years, with the highest estimates in the early twenties (Brown et al., 2001; Kessler & Berglund et al., 2005), whereas for MDD, the estimates tend to be the late twenties to the early thirties (Kessler, Berglund, et al., 2005).

Rapee and Spence (2004) suggested one caution to the interpretation of these data as meaning that SAD causes depression: SAD may predate depression solely because of its earlier age of onset, rather than because of a causal relationship. Indeed, SAD is associated with the earliest age of onset of the Axis I disorders (age at 50th percentile of age-of-onset distribution = 13; Kessler, Berglund, et al., 2005) and has been reported to be the disorder that most frequently precedes other disorders in a clinical sample (Brown et al., 2001). These findings suggest that SAD occurs before other disorders because the early age of onset is a feature of the disorder, rather than an indication that SAD is causing the other disorders that tend to follow it.

On the other hand, when MDD is secondary to other disorders, it most often follows specific phobia and SAD (deGraaf et al., 2003), suggesting at least that a specific causal pathway from SAD to MDD is more plausible than that between most other disorders and MDD. There is also evidence that the age of onset of SAD may influence the age of onset of MDD. Dalrymple and Zimmerman (2011) reported that participants with an onset of SAD in childhood were more likely to report an onset of MDD before age 18 when compared to participants with an onset of SAD in adulthood. This finding suggests that the age of onset of SAD may influence the age of onset of comorbid MDD, which could provide evidence consistent with a causal relationship between SAD and MDD. However, these results do not provide an adequate test of whether there is an association between SAD and MDD above and beyond a shared vulnerability, because no proposed shared vulnerability was measured or accounted for in these studies. We thus do not know if the age of onset of SAD would continue to predict the age of onset of MDD above and beyond a shared vulnerability. It is plausible that greater vulnerability leads to earlier age of onset of both disorders, rather than earlier age of onset for SAD specifically leading to earlier onset of MDD. Theories proposing a specific pathway from SAD to MDD are therefore consistent with available evidence, but theories proposing a shared vulnerability leading to both are just as consistent and arguably more parsimonious.

Cognitions

In addition to evidence that SAD and MDD share genetic risk, literature on the cognitions associated with each disorder suggests common cognitive features that may represent either additional shared vulnerability or a different symptom of the same vulnerability. For example, both SAD and MDD have been linked to negative self-statements and cognitive discrepancies (Dozois & Frewen, 2006; Strauman, 1989). These findings are described in more detail below in the Theorized Characterization of the Underlying Vulnerability section. Additionally, it appears that SAD and MDD interact to influence cognitive features such as attentional bias and interpretation style.

Here, we evaluate whether the interactive effect of the disorders on cognitions provides support for the shared vulnerability versus the direct causal pathway theory. Grant and Beck (2006) investigated the influence of comorbidity on attentional biases in social anxiety and dysphoria using the emotional Stroop task. The authors compared responses to this task between three groups: a

group with higher social anxiety, a group with higher dysphoria, and a group with both higher social anxiety and higher dysphoria. Based on previous research, the authors hypothesized that participants in the group with higher social anxiety would show an attentional bias to socially threatening stimuli. They predicted that the groups with higher dysphoria would show no attentional biases to any threat stimuli. To justify their hypotheses, the authors cited previous research that suggests that when anxiety and depression are comorbid, depression may counteract the attentional biases associated with anxiety (Bradley, Mogg, Miller, & White, 1995; Mogg, Bradley, Williams, & Mathews, 1993). The authors found that the group with higher social anxiety showed longer latencies to color name the social anxiety and depression threat words relative to the group with higher dysphoria and the group with higher social anxiety and higher dysphoria. Based on these results, social anxiety and depression may interact to alleviate the bias toward social and depressive threat stimuli associated with higher social anxiety. Why this would be the case remains unclear. These results suggest that attentional bias toward threat stimuli may be a feature specific to anxiety. However, in previous research depression has been associated with negative attention biases (e.g., Joormann, Talbot, & Gotlib, 2007), so it is clearly not the case that depression never confers attention bias toward negative stimuli.

In addition to associations with attentional biases, both social anxiety and depression have been linked to negative interpretative biases. Wilson and Rapee (2005) investigated the relationship between depression, social anxiety, and attributional style in a sample of treatment-seeking individuals with SAD. The participants were divided into two groups: those with and those without a comorbid mood disorder. Based on a self-report measure of interpretative style, the authors concluded that both SAD and depression were associated with more negative interpretations. Furthermore, the group with both SAD and a mood disorder reported believing their negative interpretations significantly more than the group with SAD but no mood disorder. These results suggest that social anxiety and depression may have an additive quality in producing negative interpretations. Notably, this finding (in regard to interpretation bias) contrasts with the Grant and Beck (2006) finding, in which depression seemed to reduce attention bias toward social threat. In the following section we describe one explanation for these findings within the context of theories for the comorbidity of SAD and MDD.

It appears that in some instances the addition of depression to social anxiety leads to a decrease on an index of severity (attentional bias toward threat), whereas in other cases, the addition of depression to social anxiety leads to an increase on an index of severity (negative interpretations). These findings provide further evidence that the combination of social anxiety and depression within an individual has an influence on variables such as cognitive bias and interpretation that is different than either alone. However, these results do little to strengthen support for the shared underlying vulnerability theory versus the direct causal pathway theory; both theories could be seen as consistent with the data. For example, these findings could be interpreted as evidence that MDD has a direct influence on SAD because the addition of MDD to SAD resulted in a reduction of the attention bias toward threat. However, we find it more plausible that the results are explained by both disorders being caused by greater levels of a shared underlying vulnerability. The underlying vulnerability to certain cognitions may lead to more attention bias at moderate levels of the vulnerability but less attention bias at higher levels of the vulnerability. Someone who has SAD without MDD (moderate level of vulnerability) might be biased to detect social threat in order to avoid it, whereas someone with SAD and MDD (higher level of vulnerability) may have given up trying to avoid social threat because of their more extreme negative interpretations. The interpretation of social threat as not only catastrophic but also unavoidable is more negative than viewing it as catastrophic but avoidable, yet an attention bias might only be promoted by the belief that the catastrophe can be avoided. Therefore we would expect the comorbidity of SAD and MDD to be associated with more negative interpretations but reduced attention bias toward threat. Our expectations on this point are largely driven by our characterization of the underlying vulnerability, which we expound on in the next section.

Characterization of the Underlying Vulnerability

How can we characterize the shared underlying vulnerability of SAD and MDD and how does this vulnerability, or set of vulnerabilities, give rise to the respective symptom patterns that we observe? We believe that the common vulnerability may be the presence of an excessive belief that one is not good enough. The proposition that seeing oneself

as not good enough is related to depression should be uncontroversial: Feelings of worthlessness and excessive guilt are criteria for the disorder (American Psychiatric Association, 2000). Some theorists have proposed that SAD is not related to a trait-like tendency to view oneself as not good enough (Clark & Wells, 1995), proposing that people with SAD only experience such thoughts in social situations. However, subsequent research has failed to support this assertion, instead finding that people with higher social anxiety tend to view themselves more negatively in domains apparently unrelated to social situations (e.g., Moscovitch, Orr, Rowa, Reimer, & Antony, 2009).

On the level of theory, we find the belief of being not good enough to be a plausible shared vulnerability because both disorders are related to one's status within social hierarchies, specifically feeling that one is of lower status compared to others (Gilbert, Allan, Brough, Melley, & Miles, 2002; Wilhelm & Parker, 1989). This belief would then function to influence one's response to a social defeat (perception of loss of social status), which is theorized to be a key event that can lead to a either a submissive (i.e., socially anxious) or defeat (i.e., depressive) response. We first review the psychoevolutionary theory of social anxiety and depression because it provides the basis for our hypothesis that a belief in being not good enough provides the shared vulnerability between the disorders. We then review a study that links social anxiety and depression to social defeats. Finally, we draw on relevant research from the cognitive literature that is consistent with the hypothesis that SAD and MDD are associated with cognitions related to negative views of the self.

Trower and Gilbert (1989) have proposed an evolutionary theory that conceptualizes both social anxiety and depression as strategic responses to a competitive social environment. According to this theory, individuals who have higher social anxiety feel that they are of lower status and are, thus, unlikely to achieve a dominant status within a social hierarchy. These individuals may employ a submissive strategy to avoid competition and communicate to others that they are not a threat. If this strategy is unsuccessful, an individual may use a strategy of escape or avoidance. If these strategies are still not successful, the individual may enter a depressive state of resignation or despair, in which the struggle for survival is abandoned. Psycho-evolutionary theorists have suggested that depression may be an adaptive strategy to social threat because it is associated with reduced exploratory behaviors, which may prevent further defeats (Allen & Badcock, 2003; Price, Sloman, Gardner, Gilbert, & Rhode, 1994). In a recent review, Johnson, Leedom, and Muhtadie (2012) found support for a link between feelings of subordination or submissiveness within a dominance hierarchy and anxiety (especially social anxiety) and depression across a variety of assessment modalities (self-report, observational, biological).

Weeks, Rodebaugh, Heimberg, Norton, and Jakatdar (2009) investigated a submissive cognitions model of social anxiety to test the psycho-evolutionary theory of social anxiety. The authors proposed that, based on evolutionary theories of social anxiety and depression, social anxiety should be associated with measures related to submissive cognitions. The authors found support for a model in which measures related to submissive cognitions loaded on a higher order submissive cognitions factor. Furthermore, based on factor scores derived from this factor, submissive cognitions were found to be more related to a measure of social interaction anxiety than to either of two measures of generalized anxiety symptoms. Submissive cognitions also mediated the relationship between social comparison and submissive behaviors. These findings suggest that social anxiety is indeed related to submissive cognitions, which are related to submissive behaviors. The fact that submissive cognitions mediated the relationship between social comparison and submissive behaviors could indicate that only some individuals who are faced with a lower social rank will tend to respond with submissive behaviors. These individuals may have an underlying vulnerability to submissive cognitions, which may be a shared underlying vulnerability to social anxiety and depression.

Gilbert et al. (2002) presented evidence that is consistent with the theory that anxiety and depression are related to defeats within a social hierarchy. The authors investigated the relationship between social comparison, defeat, and scales of anhedonic depression and anxious arousal. All variables were measured through self-report questionnaires. Structural equation modeling results suggested a higher association of defeat with anhedonic depression in comparison to anxious arousal. Social comparison was also related to defeat and was nearly significantly related to anhedonic depression. The authors suggested that it may be evolutionarily adaptive for defeats to lead to lower positive affect (measured by the anhedonic depression scale in this study) so as to lower activity and explorative behavior, thus helping the individual to avoid

further defeating interactions. Though this study was cross-sectional and does not provide information on causality, plausible causal relationships can be considered. It seems plausible that defeats could lead to a depressive-type response that would be associated with lower positive affect and reduced exploratory behaviors such as social contact, as has been suggested by authors such as Allen and Badcock (2003) and Price et al. (1994). We also theorize that submissive cognitions or a general belief in being less than others may mediate the relationship between defeats and a depressive-type response. Such mediation would suggest that certain individuals are more prone to develop depression when a defeat occurs; however, this theory needs to be tested against the alternative theory that certain individuals are more prone to defeats in general. It could be that one plausible route from social anxiety to depression is that social anxiety arises out of perceived low-rank status, which may make defeats more likely, thus leading to increased depression and decreased positive affect.

Findings from research on self-statements (positively and negatively valenced adjectives that are rated in terms of applicability to the self) in relation to SAD and MDD are consistent with the hypothesis that both disorders share a vulnerability to negative beliefs about the self. It appears that both negative and positive self-statements are associated with social anxiety and depression but that the symptom clusters differ in the degree to which each type of self-statement is related. Dozois and Frewen (2006) measured the distance between self-statements as an indication of the cognitive availability of these types of statements. The authors found that both participants with MDD and participants with SAD reported more distance among positive self-statements and less distance among negative self-statements as compared to nonpsychiatric and anxiety control groups (diagnosed with an anxiety disorder other than SAD). The decreased distance between negative self-statements was interpreted as an indication that negative statements are more readily available and seen as more related to the self for those with either MDD or SAD.

Studies on self-discrepancies by Strauman (1989) and Weilage and Hope (1999) provide more evidence for negative views of the self in those with SAD and MDD. In Strauman participants diagnosed with SAD reported greater discrepancy between their actual personal attributes and their "ought" personal attributes (perceptions of how others think they should be), whereas participants diagnosed with MDD reported a greater discrepancy between their actual personal attributes and their ideal attributes (state to which individual personally aspires). Additionally, participants with MDD showed increases in dejected mood following ideal self-discrepancy priming, whereas participants with SAD showed increases in agitated mood following ought self-discrepancy priming. In evaluating the relation of this study to comorbidity, it is important to note that no SAD and depression comorbidity was present in the sample.

In a study that attempted to replicate the findings of Strauman (1989) while accounting for comorbidity, Weilage and Hope (1999) included individuals with both SAD and dysthymia to assess the influence of comorbidity on self-discrepancies. The authors found that individuals with both SAD and dysthymia reported higher actual–ideal and higher actual–ought discrepancies compared to normal controls; however, individuals with dysthymia alone reported equivalent levels of actual–ought discrepancy relative to those with SAD alone. Furthermore, individuals with dysthymia alone did not differ from normal controls in actual–ideal discrepancy. These results partially conflict with the results of Strauman. Overall, however, the picture provided by these data is that both SAD and depression or dysthymia are related to increased cognitive discrepancy. It also appears that SAD plus dysthymia confers more cognitive discrepancy than either condition alone. These results are consistent with the hypothesis that both disorders share a vulnerability to certain cognitions such as a belief that one is inferior or less than others. This shared vulnerability may explain the high rate of comorbidity between the disorders, and individuals who are comorbid for both conditions may be individuals who have a greater cognitive vulnerability (i.e., greater cognitive discrepancy, for example).

Potential Causal Pathways from SAD to MDD

Although we cannot rule out that the following data are better explained by a shared underlying vulnerability to both disorders, we feel it is important to present the following discussion of theories for potential causal pathways between the disorders (including proposed intervening variables), because they have received attention in the literature. We first discuss three theories that have at best modest

support and have not been tested rigorously with comparison to competing theories (helplessness–hopelessness theory, exhaustion response theory, and behavioral avoidance theory). We then discuss two theories that describe potential intervening variables between SAD and MDD (positive affect theory and early life experiences theory); we find these latter two potential pathways as more plausible than those proposed by the first three theories. More precisely, it seems to us that the latter two theories might better explicate the same phenomena the first three theories attempt to capture.

Helplessness–Hopelessness Theory

Mineka, Watson, and Clark (1998) developed a model that integrates the hopelessness theory of depression with the perceived uncontrollability associated with anxiety (Wells & Carter, 2001). Although this theory does not relate to *social* anxiety specifically, we still find the theory relevant, because fears about social situations may behave in a similar fashion to fears in general, though a direct test of this assumption is needed. This model suggests that individuals who are uncertain about their ability to control important outcomes will be most likely to experience anxiety without depression, whereas individuals who are certain of both helplessness and occurrence of negative outcomes will experience the hopelessness of depression (Alloy, Kelly, Mineka, & Clements, 1990). This model is supported by evidence that anxiety is associated with threat or danger and is thus related to uncontrollability of events, whereas depression is often associated with a loss (e.g., Brown, Harris, & Eales, 1993). This model could explain the temporal relationship between the disorders because helplessness could come first (from a vulnerability to anxiety) and hopelessness could develop after a specific negative outcome occurs.

In an experience-sampling study of the helplessness–hopelessness theory, Swendsen (1997) assessed participants five times per day for a week regarding experience of negative events, attributions, and anxiety and depression. Swendsen found partial support for the helplessness–hopelessness theory; increases in hopeless attributions predicted increases in residual depressed mood following negative life events. However, control attributions (helplessness) did not predict residual anxiety scores. We were able to find only two additional specific tests of this theory (Swendsen, 1998; Waikar & Craske, 1997), both of which found only partial support for the theory. The hopelessness–helplessness theory is a promising theory with little direct testing and only partial support from the testing completed thus far. More specifically, a direct test of whether helplessness and hopelessness play a causal role in the development of social anxiety and depression symptoms is sorely needed.

Exhaustion Response Theory

Some authors have proposed that chronic anxiety may lead to an exhaustion response that eventually results in depression (e.g., Akiskal, 1990). Kessler, Stang, Wittchen, Stein, and Walters (1999) investigated this theory, predicting that if this were true in regard to SAD the rates of depression would increase as the duration of SAD increases. Additionally, the authors predicted that if SAD were a true risk factor, only current SAD, but not remitted, would predict depression (if SAD were a marker of vulnerability rather than a specific risk factor for depression, remitted SAD might continue to relate to the risk of depression). Kessler et al. (1999) reported that current SAD predicted mood disorders overall with an increased odds ratio for SAD with three or more social fears compared to one fear. For individuals with only one social fear (e.g., public speaking), SAD was not related to the severity or course of mood disorders. Remitted SAD had no significant effect in predicting the first onset of either mood disorders or dysthymia and modest effects in predicting major depression. However, the relationship between SAD and mood disorders did not vary significantly with time since the first onset other than for those with same-year onsets (i.e., both disorders started within the same year). These findings provide partial support for the above predictions, though the lack of relationship between the duration of SAD and rates of depression casts some doubt on the exhaustion theory. Additionally, the exhaustion theory appears to relate only to more severe or generalized cases of SAD and may not be able to explain co-occurrence with depression in less severe cases or in the case of specific SAD. We speculate that SAD does not produce exhaustion per se but rather that, for reasons including SAD severity but not exclusive to SAD severity, some people with SAD give up avoiding social exclusion and thus become more vulnerable to depression. We elaborate on this idea further after concluding our review of specific theories of how SAD leads to depression.

Behavioral Avoidance Theory

It has been proposed that behavioral avoidance may be the primary link between social anxiety and depression (Moitra, Herbert, & Forman,

2008). According to this theory, social anxiety leads to behavioral avoidance, which in turn leads to depression. Moitra et al. tested this theory in a sample of treatment-seeking individuals assessed at baseline, six weeks into treatment, and at the end of treatment. They found that behavioral avoidance partially mediated the relationship between social anxiety and depression symptoms. Changes in behavioral avoidance from pretreatment to midtreatment were significantly correlated with midtreatment to posttreatment changes in depressive symptoms.

This theory provides support for an intermediate variable or condition along the path between the two disorders. Behavioral avoidance may mediate the relationship, or, alternatively, the consequences of behavioral avoidance could activate an underlying vulnerability to depression. Finally, there are likely other contributing factors besides behavioral avoidance because it explained only part of the variance in depression in Moitra et al. (2008). Notably, the concept of behavioral avoidance is very similar to that of reduced social contact and positive affect, as well as the psychoevolutionary theory of SAD and MDD, as reviewed above. Specifically, the belief that one is not good enough or of low status could lead to behavioral avoidance as a strategy to avoid further defeats.

Positive Affect

Lower positive affect, once thought to be a unique feature associated with depression, has also been linked to higher social anxiety. We propose that lower positive affect functions as both an underlying vulnerability as well as a consequence of social anxiety and depression. First, we review evidence that supports the shared relation to lower positive affect. Second, we consider the possibility that both disorders relate to lower positive affect because of deficits in social activities. Third, we consider other explanations for the shared relation, such as a shared underlying vulnerability to lower positive affect. Figure 8.1 depicts the theoretical pathways that we consider during this discussion.

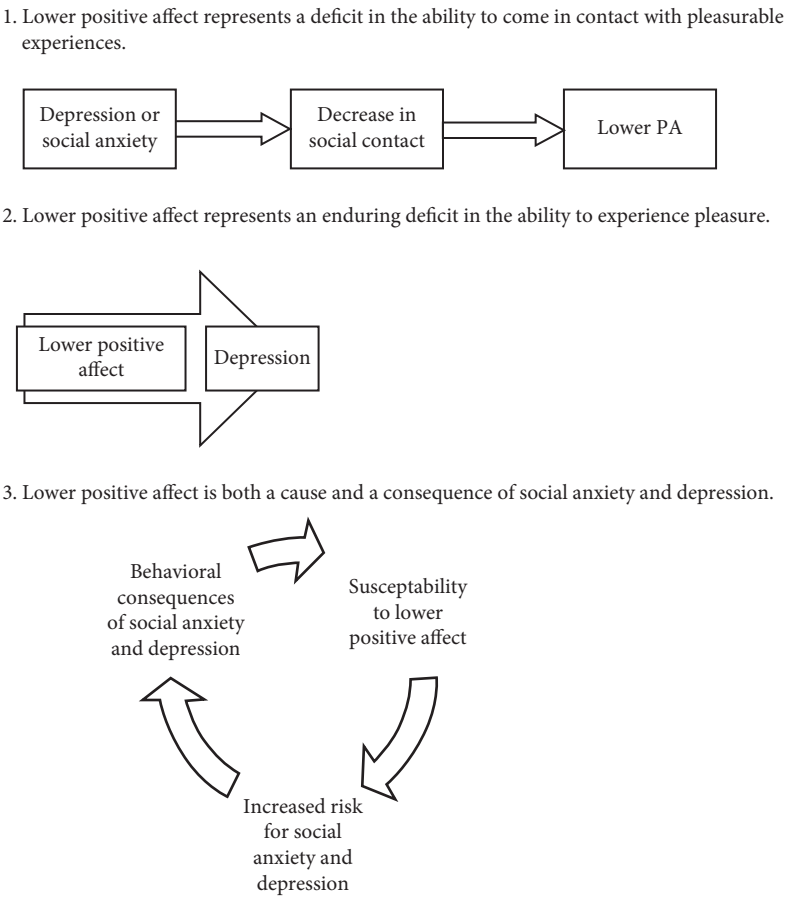

Figure 8.1 Potential causal pathways among social anxiety, depression, and lower positive affect.

In proposing alternatives to the *Diagnostic and Statistical Manual of Mental Disorders* (fourth edition, text revision; American Psychiatric Association, 2000) categorical system, researchers have modeled shared relationships with basic underlying traits such as positive and negative affect (e.g., Watson, 2009). For example, the tripartite model of anxiety and mood disorders models the common relationship to higher negative affect that is characteristic of the anxiety and mood disorders, as well as the unique relationship to lower positive affect that is characteristic of depression (Clark & Watson, 1991). This model has also been adapted to account for accumulating research that shows that generalized SAD is unique from the other anxiety disorders in that it also shows a consistent relation to lower positive affect (Brown, Chorpita, & Barlow, 1998).

The shared relation of social anxiety and depression to positive affect has been a consistent finding in the literature (Brown et al., 1998; Hughes et al., 2006; Kashdan, 2004; Kashdan & Steger, 2006; Naragon-Gainey, Watson, & Markon, 2009; Watson, Clark, & Carey, 1988), both at the symptom level (Watson et al., 1988) and the diagnostic level (Brown et al., 1998). Watson et al. reported that negative affect was related to the majority of the anxiety and depression symptoms measured, whereas positive affect was related to 11 of 20 depression symptoms but only 3 of 33 anxiety symptoms. These three symptoms (*nervousness, being in a crowd*, and *speaking in public*) were all related to social anxiety. Indeed, positive affect correlated with MDD and dysthymia diagnoses as well as SAD diagnoses. Brown et al. found similar results; the authors reported that higher negative affect related to generalized anxiety disorder, SAD, panic disorder, and MDD, whereas lower positive affect related to SAD and MDD.

In an attempt to explain why SAD and MDD are related to lower positive affect, researchers have suggested that the deficits in social contact that are characteristic of these disorders may produce decreases in positive affect. Both higher social anxiety (Rodebaugh, 2009; Schneier et al., 1994) and higher depression (Joiner & Coyne, 1999) have been associated with reduced social contact. Additionally, sociability and social interactions have both been shown to relate to positive affect (Brown, Silvia, Myin-Germeys, & Kwapil, 2007; Costa & McCrae, 1980; Vittengl & Holt, 2000), suggesting that social contact could mediate the relationship between these disorders and lower positive affect. The first model in Figure 8.1 depicts this relationship.

A study by Kashdan and Steger (2006) on the relationship between trait social anxiety, daily social anxiety, and positive events provides some support for the idea that social anxiety is related to reduced positive affect because of a lack of contact with positive affect-inducing activities. The authors found that trait social anxiety was inversely associated with daily positive emotions and daily positive events, above and beyond variance explained by trait negative affect. The relationship between trait social anxiety and daily positive events remained significant above and beyond variance explained by depression, whereas the relation to daily positive emotions was reduced to nonsignificance. The authors also found that individuals in the group with higher social anxiety reported 39% fewer daily positive events than those in the group with lower social anxiety. Furthermore, individuals with higher social anxiety with greater daily social anxiety (defined as at least one standard deviation above the mean) reported 24% fewer daily positive events than individuals with higher social anxiety with less daily social anxiety. These findings provide some support for the hypothesis that higher social anxiety is related to lower positive affect because of decreases in social activities. However, the nonsignificant association between trait social anxiety and daily positive emotions above and beyond depression is unexpected given the documented independent relationship between social anxiety and positive affect.

These findings suggest that within the context of higher social anxiety and depression, lower positive affect could result from the deficits in social contact associated with these symptoms. If this were the case, a causal pathway could link these symptoms in the following order: (1) social anxiety, (2) reduced social contact, (3) reduced positive affect, (4) increased depression. Once an individual was depressed, positive affect would likely be further reduced due to the association between depression and reduced social contact. If this were the case, this relationship could at least partly explain the high rate of association between the disorders.

Although it seems likely that deficits in social contact lead to reductions in positive affect for those with higher social anxiety and depression, lower positive affect may function as an underlying vulnerability that confers risk to both disorders, rather than as a consequence of either disorder (second model in Figure 8.1). As noted above, research on the heritability of extraversion and neuroticism (traits that are strongly related to positive and negative affect, respectively) suggests that one's genetic makeup

confers risk for certain levels of positive and negative affect that then lead to various forms of psychopathology (Bienvenu et al., 2007). Therefore, a susceptibility to lower positive affect (or extraversion) may exist as both an enduring underlying trait as well as a feature that is exacerbated by consequences of the disorders such as reductions in social activities (depicted in the third model in Figure 8.1).

Though not described in terms specific to positive affect, a combination of the evolutionary and behavioral theories described above can be used to explain how social anxiety, depression, reduced social contact, and positive affect might have a tendency to influence each other. In the face of a social threat or the threat of social exclusion, a depressive withdrawal or submissive social anxiety response may have been evolutionarily adaptive because such responses would help one to avoid further exclusion and promote self-reflection designed to avoid further difficulty (Allen & Badcock, 2003; Price et al., 1994). This response would be associated with a reduction in the reward system such that exploratory and approach behaviors would be reduced. The reduction in these behaviors would be associated with lower positive affect, which would likely lead to temporary further decreases in positive affect as a result of reduced social contact. If such a system were to be adaptive, it would need an exit point leading to more normative behaviors: For example, a person might resume exploration and seeking of reward once it was clear that social exclusion was no longer likely, perhaps because current social rank was clearly defined and defensible.

In the absence of clear evidence that social exclusion is no longer a danger, the relationship between perceived social exclusion, reduced exploratory behaviors, and reduced positive affect could be seen as a behavioral trap. The term *behavior trap* describes a situation in which an individual's naturally occurring behavior is reinforced and this reinforcement leads to even higher rates of the original behavior, which is then further reinforced (Baer & Wolf, 1970). The result of this cycle from a negative reinforcement perspective is that the individual will end up receiving more of the unpleasant stimulus he or she was trying to avoid. In this example, an attempt to cope with a threat of social exclusion leads to reduced contact, which might paradoxically increase the threat of further exclusion (e.g., because the individual has not maintained or strengthened existing ties). Once an individual has responded with a submissive or withdrawal technique, that person may be more likely to experience further depression and social anxiety because of further loss of social bonds. It could be that certain individuals, in certain contexts or cultures, are able to use the submissive or depressive techniques in a temporary, effective manner but others tend to fall into a behavioral trap that leads to chronic depression or social anxiety, which would be equivalent to MDD, SAD, or their combination. See Figure 8.2 for a visual depiction of this theory. We believe that this theory is compatible with the hypothesis that SAD and MDD share a vulnerability to certain beliefs such as the belief that one is inferior to others; we propose that this vulnerability may determine whether one is able to use a submissive or withdrawal response effectively or whether one is drawn into a behavior trap. We suggest that those with a cognitive vulnerability would be more likely to be drawn into the behavior trap because they would be more likely to interpret an interaction as a social exclusion or defeat.

Early Life Experiences

In addition to positive affect, early life experiences, such as bullying, have been explored as a possible cause of social anxiety and depression and have also been explored as a mediator between the two conditions. We suspect that such a relationship would be related to the constellation of social contact, positive affect, social anxiety, and depression noted above. Specifically, peer exclusion may function as one type of social defeat that could lead to the behavior trap described above. In one instance of related research, Gazelle and Rudolph (2004) investigated the role of the environment in the relationship between anxious solitude and peer exclusion in fifth- and sixth-graders, theorizing that peer exclusion may mediate the relationship between anxiety and depression. The authors found that for anxious boys with high anxious solitude, high peer exclusion was associated with increased levels of depression over time, whereas low exclusion was associated with decreasing levels of depression over time. For girls, high anxious solitude and high peer exclusion predicted elevated depressive symptoms. The relationship between anxious solitude and depression did not differ depending on high versus low exclusion as it did in boys. It may be that social anxiety leads to depression only under certain circumstances, such as when a stable negative event of a specific type (e.g., peer exclusion) happens to a person with elevated tendencies toward social anxiety, leading to depression. These findings are consistent with an intervening variable that is related to

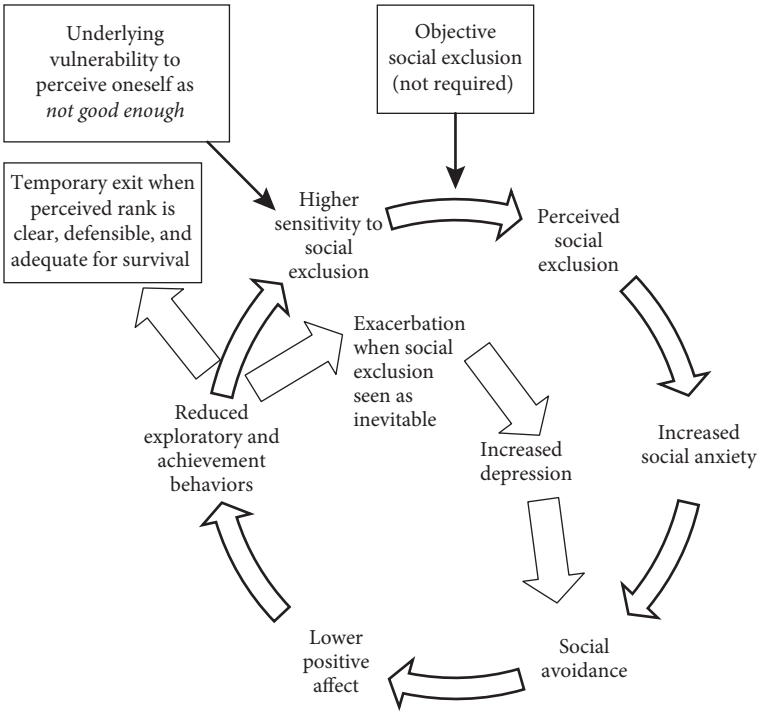

Figure 8.2 Depiction of the behavioral trap between lower positive affect, social anxiety, and depression.

social anxiety and has a direct path to depression; however, further testing is required to determine whether this additional causal pathway is not better accounted for by an underlying shared vulnerability. It might be that peer exclusion mediates the relationship between social anxiety and depression, for example; yet it seems equally plausible that a vulnerability that increases a person's tendency to view peer exclusion as catastrophic might confer vulnerability to social anxiety to begin with and promote the development of depression when such exclusion occurs.

We propose that the potential intervening variables of lower positive affect and peer exclusion deserve further testing to determine whether they function as mediating variables in a causal pathway from SAD to MDD or whether they are related to an underlying vulnerability. To continue our discussion of whether a shared underlying vulnerability versus direct causal pathways better explains the comorbidity between SAD and MDD, we now turn to research on treatment response.

Treatment

Research on treatment response that considers the comorbidity between SAD and MDD has the potential to inform whether additional causal pathways exist above and beyond a shared underlying vulnerability. We review research from the treatment literature that could be interpreted as support for either the shared underlying vulnerability theory or the direct causal pathway theory. We suggest that, as it stands, the treatment literature does little to advance one theory over the other.

There are four main findings from the treatment literature that are relevant to our discussion of theories for the comorbidity between SAD and MDD: (a) Cognitive behavior therapy (CBT) for SAD has been shown to alleviate comorbid depression (Erwin, Heimbrg, Juster, & Mindlin, 2002); (b) individuals with both SAD and MDD have been rated as having more severe social anxiety by clinician rating (Joormann, Talbot, & Gotlib, 2007); (c) individuals with both disorders have shown an increase in social anxiety symptoms posttreatment, and baseline scores on a depression measure have predicted the worsening of social anxiety symptoms from termination to follow-up (Marom, Gilboa-Schechtman, Aderka, Weizman, & Hermesh, 2009); and (d) Decreases in social anxiety symptoms mediated decreases in depression but decreases in depression did not mediate decreases in social anxiety (Moscovitch, Hofmann, Suvak, & In-Albon, 2005). In relation to finding (d), it is important to note that the participants in this study were recruited specifically for SAD, not MDD. Findings (a) and (d) could

be seen as evidence for a direct pathway from SAD to MDD, because treatment for SAD alleviated depression symptoms or predicted decreases in depression symptoms. However, we suggest that what is needed is a test that includes the measurement of the shared underlying vulnerability to see whether decreases in SAD symptoms or treatment of SAD continue to predict decreases in depression symptoms above and beyond the underlying vulnerability. It could be that treatment for SAD addresses underlying tendencies for both disorders. Regarding findings (b) and (c), although these results could be seen as support for depression having a direct influence on social anxiety, we believe that it is just as likely that the presence of depression in those with SAD is a marker for greater levels of a shared underlying vulnerability.

Conclusions

We believe that evidence exists to suggest that the comorbidity of SAD and MDD is at least partly explained by a common underlying vulnerability that is likely largely inherited. There are likely other common vulnerabilities beyond genetics and potentially direct causal pathways between the disorders. The research reviewed above suggests to us that a common underlying vulnerability to both disorders is conferred by genetics and enduring heritable traits such as tendencies toward negative and positive affect. These heritable traits may influence the cognitive styles that relate to social anxiety and depression. An individual whose genetic makeup predisposes her to experience more negative affect and less positive affect may be at increased risk for the development of a depressive disorder or SAD. Tendencies toward higher negative affect and lower positive affect will likely influence her cognitions and level of approach and exploratory behaviors. These tendencies may increase the risk for social threats such as bullying or social exclusion. Under conditions of perceived social threat, she may respond with a submissive strategy and a further reduction in reward responsiveness and exploratory behaviors. These behaviors may lead to further reductions in social rank and decreases in the experience of positive affect. This cycle may lead to the withdrawal tactic that is characteristic of a depressive state. When these tactics are employed in a chronic, maladaptive fashion, they may be characteristic of clinical levels of social anxiety and/or depression.

Assessment and Intervention Strategies

Given that comorbidity between SAD and MDD is both important and relatively prevalent, a common question is how to assess and treat this comorbidity. For the assessment of SAD and MDD we recommend the use of a few self-report instruments as well as a structured interview. For self-report questionnaires, we recommend the Social Interaction Anxiety Scale (SIAS) and the Social Phobia Scale (Mattick & Clarke, 1998) for SAD and the Beck Depression Inventory-II (Beck, Steer, & Brown, 1996) for MDD. We recommend omitting the reverse-scored items when calculating a total for the SIAS because previous research indicates that these items decrease the overall validity of the scale (Rodebaugh et al., 2011). We recommend a score of 28 as a cutoff on the straightforward SIAS items to indicate probable SAD; this score is comparable to the existing cutoff of 34 for the original total of the SIAS (Brown et al., 1997; Heimberg, Mueller, Holt, Hope, & Liebowitz, 1992; Rodebaugh et al., 2011). Importantly, utilizing both the SIAS and the Social Phobia Scale together will give a comprehensive picture of the social anxiety symptom severity. For the Beck Depression Inventory-II, the authors recommend the following cutoffs: zero to 9 (*minimal depression*), 10 to 18 (*mild depression*), 19 to 29 (*moderate depression*), and 30 to 63 (*severe depression*; Beck et al., 1996).

In addition to self-report instruments, we strongly recommend the use of a structured interview such as the MINI International Neuropsychiatric Interview, Version 5.0 (Sheehan et al., 1998) or the Structured Clinical Interview for DSM-IV (Spitzer, Williams, & Gibbon, 1995). A structured interview will be helpful in determining whether the client meets criteria for a *Diagnostic and Statistical Manual for Mental Disorders* (fourth edition) diagnosis of SAD and/or MDD as well as helping to determine the duration of the disorders. The self-report instruments are helpful for a continuous measurement of the symptomatology, which can indicate level of severity.

For intervening with clients who meet criteria for both MDD or dysthymia and SAD, we recommend beginning with a cognitive behavioral intervention for SAD. CBT for SAD is an effective treatment for alleviating social anxiety symptoms (Clark et al., 2003, 2006; Zaider, Heimberg, Roth, Hope, & Turk, 2003) and has also been shown to alleviate comorbid depression (Erwin et al., 2002). Instead of attempting to determine which disorder is primary, which is often difficult or impossible, we recommend beginning with CBT for SAD for the majority of clients and beginning with a treatment for depression only when a client's depression

is so severe as to demand immediate attention. For targeting depression symptoms either before beginning CBT for SAD or treating residual depression after a course of CBT for SAD, we recommend cognitive therapy, behavioral activation, or other CBT treatments designed specifically for depression. Cognitive therapy or CBT for depression should include cognitive restructuring as well as behavioral activation interventions. Behavior activation alone has produced promising results for alleviating depression (Dimidjian et al., 2006; Dobson et al., 2008). Fortunately, there is substantial overlap between behavioral activation and CBT for SAD in the behaviors that are recommended to the client. For example, in behavioral activation the primary objective is to help the client become more active, which nicely mirrors the primary goal of CBT for SAD of having the client participate in exposure to social activities. In this way, we expect that, for many clients, treatment for SAD will alleviate comorbid depression either directly through the increase in activity or indirectly as the decrease in social anxiety symptoms leads to an improved social life.

Another important point to consider is that clients with both SAD and MDD may have more severe symptoms than clients with either disorder by itself (Joormann, Talbot, & Gotlib, 2007). Additionally, comorbid clients may be more likely to show increases in social anxiety symptoms posttreatment, and this risk may be greater for those with higher levels of depression at the beginning of treatment (Marom et al., 2009). However, previous research suggests that comorbid depression does not interfere with SAD treatment and vice versa (Erwin et al., 2002; Kashdan & Roberts, 2011). Clinicians should be encouraged that treatment for SAD is likely to be effective for clients with and without comorbid depression but may want to consider the severity of depression when planning for the length of treatment and planning for relapse prevention with comorbid clients.

Future Directions

There are many questions that remain unanswered in relation to the high degree of overlap between SAD and MDD. Much of the research we reviewed here focuses on shared features of the disorders, but research on which features may be unique to the disorders could be further developed. For example, we found very little research that addresses whether either disorder has a unique genetic risk above and beyond shared genetic risk, but this may be an area that warrants further testing. We propose that research regarding genetic risk for dimensional constructs underlying diagnoses (e.g., degree of social anxiety, degree of depressed mood) might allow greater power for distinguishing unique genetic variance. Along similar lines, further research on unique environmental influences on each disorder would also help to explicate any differences in etiology between the disorders.

Given the high degree of association between these disorders and the theorized causal pathways between the two, one of the most interesting areas for future research might be to investigate cases in which the disorders occur independently. These cases may tell us more about the relationship between these two disorders by hinting at conditions that need to be present for both to occur. Additionally, we found many instances in the literature in which MDD was theorized to be secondary or a consequence of SAD but hardly any suggestion of SAD being a consequence of MDD. Nevertheless, the treatment literature provided some suggestion of a bidirectional causal link between the two disorders. Further investigation of when SAD may be secondary to MDD should be undertaken by future researchers to test whether there is a causal pathway from MDD to SAD. Finally, researchers in each of the literature areas investigated should consider how their results may explain the association between social anxiety and depression. For example, research in the cognitive area provides evidence on shared and unique cognitive features but little description of how the cognitive style associated with one disorder may relate to the symptomatology of the other disorder. For example, it could be that the negative cognitions associated with depression may make social anxiety more likely because persons who feel that they are worthless may be more likely to try to hide their self from others and believe that they are more likely to be rejected. Attempts to move research on the comorbidity between SAD and MDD in this direction will help to reveal the specific mechanisms that explain the high degree of association between these disorders.

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CHAPTER

9

Important Issues in Understanding Comorbidity Between Generalized Anxiety Disorder and Major Depressive Disorder

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Abstract

The comorbidity of anxiety and mood disorders has been of great interest to psychopathology researchers for the past 25 years. One topic—the comorbidity of generalized anxiety disorder (GAD) and major depressive disorder (MDD)—has received considerable attention, in part because it has raised fundamental nosological issues regarding whether GAD should continue to be categorized as an anxiety disorder or whether it should be recategorized as a mood disorder. We review the logic for reclassifying GAD with the mood disorders as well as what we believe to be even more compelling reasons for why it should be retained as an anxiety disorder. In doing so, we review three different kinds of comorbidity—cross-sectional, cumulative (lifetime), and sequential. We also discuss overlaps and distinctions in what is known about the etiology of GAD and MDD and how their somewhat different cognitive and neurobiological profiles bear on these issues of classification. Finally, we briefly discuss what some of the treatment implications may be for individuals with comorbid GAD and MDD.

Key Words: generalized anxiety disorder, major depressive disorder, comorbidity, nosological issues, mood disorders, anxiety disorders, treatment implications

Background

Decades of epidemiological research have demonstrated that high levels of comorbidity are the norm rather than the exception within the realm of the emotional disorders (e.g., Krueger & Markon, 2006; Mineka, Watson, & Clark, 1998). For example, high rates of comorbidity between major depressive disorder (MDD) and generalized anxiety disorder (GAD) have become a topic of especially great interest for psychopathology researchers in recent years; this topic is the focus of the current chapter. MDD and GAD not only share a number of phenotypic features (e.g., insomnia, fatigue, repetitive thought) but also have been shown to exhibit considerable co-occurrence in both epidemiological and clinical samples (e.g., Brown, Campbell, Lehman, Grisham, & Mancill, 2001; Kessler, Chiu, Demler, & Walters, 2005). Furthermore, as reviewed later, studies that have modeled the associations between symptoms and diagnoses of emotional disorders have quite consistently found that MDD and GAD load most strongly on a single higher-order distress factor rather than on separate mood and anxiety disorder factors (e.g., Krueger & Markon, 2006; Watson, 2005). Together, these results suggest that the overlap between MDD and GAD is substantial. Consequently much research has been conducted in an effort to understand why such high rates of comorbidity between MDD and GAD occur and what the implications are for how these two disorders should be conceptualized.

In this chapter, we review highlights of the literature on comorbidity between MDD and GAD. Throughout the chapter, we discuss various ways in which this comorbidity manifests itself and describe different etiological models that have been

proposed to explain why this substantial comorbidity occurs. We also review some of the nosological issues that have been raised surrounding the high rates of comorbidity between GAD and MDD. Furthermore, we briefly discuss several important issues regarding the somewhat different cognitive and neurobiological profiles of these two disorders. Finally, we also touch on some possible therapeutic implications of the comorbidity between MDD and GAD. Throughout we highlight questions for further research that are important to address in order to advance the field.

Understanding the Apparent Rise in Comorbidity Between MDD and GAD

In order to fully comprehend the current rates of comorbidity between MDD and GAD, it is important to first take into consideration the changes in the diagnostic criteria for GAD that have occurred between the third (revised) and fourth editions of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM). The criteria for GAD underwent major revisions between DSM-III-R (1987) and DSM-IV (1994), and these changes provide a key context for understanding the high levels of comorbidity between MDD and GAD. One critical change with DSM-IV was the elimination of the autonomic hyperactivity symptoms from the diagnostic criteria for GAD. Even though this change resulted in increased reliability in the diagnosis of GAD and somewhat reduced rates of comorbidity between GAD and other anxiety disorders (Mennin, Heimberg, Fresco, & Ritter, 2008), it also served to increase the overlap in the diagnostic criteria for GAD and MDD. For example, in DSM-IV, a majority of the physical symptoms associated with GAD (e.g., restlessness, fatigue, and difficulty sleeping and concentrating) are also included in the symptom list for MDD. Not surprisingly, the increase in overlapping diagnostic criteria for MDD and GAD made it more likely that individuals would be diagnosed with both disorders. At the same time, this symptom overlap somewhat obscured the meaning of comorbidity between MDD and GAD. As we discuss below, these complicating factors have led some to seriously question the diagnostic validity of the distinction between GAD and MDD as well as whether GAD should be placed in the depressive disorder rather than the anxiety disorder category.

Another diagnostic feature of GAD that may have obscured our understanding of the extent to which GAD co-occurs with MDD is the diagnostic hierarchy rule for these two disorders (Lawrence, Liverant, Rosellini, & Brown, 2009). First introduced in DSM-III-R and retained in DSM-IV, the diagnostic hierarchy rule stipulates that GAD cannot be diagnosed if it occurs exclusively during MDD or another mood disorder. This rule was implemented in order to foster diagnostic parsimony, but it may lead to an underestimation of the true rates of comorbidity between GAD and MDD. For example, in a clinical outpatient sample, Brown et al. (2001) found that GAD was comorbid with a current principal diagnosis of MDD in only 5% of cases when the diagnostic hierarchy rule was applied. However, when the diagnostic hierarchy rule was ignored, GAD was comorbid with a current principal diagnosis of MDD in 67% of cases. Furthermore, research suggests that individuals with symptoms of GAD that occur only during the course of a major depressive episode exhibit similar levels of psychopathology and functional impairment as do those with comorbid MDD and GAD based on the diagnostic hierarchy rule (e.g., Lawrence et al., 2009). Together, these findings have led some researchers to question the validity and utility of the diagnostic hierarchy rule. Consistent with this notion, in recent years many studies of the comorbidity between MDD and GAD, including a number of those cited in this chapter, have not applied the diagnostic hierarchy rule in diagnosing GAD (e.g., Kendler, Gardner, Gatz, & Pedersen, 2007; Kessler et al., 1996; Moffitt, Harrington, et al., 2007).

Cross-Sectional, Cumulative, and Sequential Comorbidity

Cross-Sectional Comorbidity

In referring to the co-occurrence of two or more disorders, comorbidity can actually manifest in a number of ways depending on the time course considered. Here we present the results for three forms of comorbidity—cross-sectional, cumulative, and sequential comorbidity—in order to provide a fairly comprehensive overview of issues in the comorbidity between MDD and GAD. Cross-sectional comorbidity is defined as meeting criteria for two disorders within the same time-frame (e.g., the past year) (Moffitt, Harrington, et al., 2007). Overall, there is evidence of relatively high cross-sectional comorbidity between MDD and GAD using DSM-III-R diagnoses. For example, in the National Comorbidity Survey (NCS), a nationally representative survey of individuals between the ages of 15 and 54 in the United States using DSM-III-R–based diagnoses, the odds ratio (OR) for MDD

and GAD being comorbid within the past year was 8.2 (Kessler et al., 1996). Thus an individual with a diagnosis of MDD within the past year had 8.2 times the risk of also having a diagnosis of GAD within the same 12-month period versus an individual without a diagnosis of MDD. More specifically, in the original NCS, 15.4% of individuals with 12-month MDD also met the criteria for GAD within the same time period.

The prospective birth cohort design of the Dunedin Multidisciplinary Health and Development Study permitted a more fine-grained examination of cross-sectional and sequential comorbidity between MDD and GAD at different ages. Participants in this study were all born in Dunedin, New Zealand, between April 1, 1972, and March 31, 1973; they were assessed every two to three years since birth (the latest assessment phase was at age 38). When participants were 18, 21, 26, and 32 years of age, Moffitt, Harrington, et al. (2007) examined the issue of cross-sectional MDD-GAD comorbidity by comparing rates of comorbid diagnoses of MDD and GAD (using DSM-IV diagnoses) within the same year. With increasing age, rates of MDD with comorbid GAD increased, namely from 8% at age 21 to 30% at age 32. However, rates of GAD with comorbid MDD decreased slightly with age, from 88% at age 18 to 63% at age 32. In other words, at age 18, nearly all individuals with GAD (88%) had comorbid MDD; but at age 32, only 63% of individuals with GAD had comorbid MDD. Across all ages, rates of GAD with comorbid MDD were greater than rates of MDD with comorbid GAD.

Cumulative (Lifetime) Comorbidity

Comorbidity can also manifest as cumulative comorbidity, in which both disorders occur but not necessarily within the same period of time (Moffitt, Harrington, et al., 2007). Assessments of cumulative (lifetime) comorbidity provide a more accurate estimate of comorbidity across the lifetime than do those of cross-sectional comorbidity because, by focusing on a limited time frame, cross-sectional assessments may significantly underestimate the degree to which an individual experiences multiple disorders during his or her life. In general, there is strong evidence of cumulative comorbidity between MDD and GAD. For instance, in the NCS, 17.2% of individuals with lifetime MDD also had a lifetime diagnosis of GAD (OR = 7.5 for lifetime comorbidity of MDD and GAD at the original NCS baseline assessment; Kessler et al., 1996). In addition, there were also substantial associations between lifetime diagnoses of MDD and GAD at the 2001–2003 NCS follow-up assessment that occurred approximately 10 years later after the baseline NCS (OR = 6.6) (Kessler et al., 2008).

Similarly, in the Dunedin study, Moffitt, Harrington, et al. (2007) examined comorbidity between lifetime diagnoses of MDD and anxiety disorders that were made between the ages of 11 and 32. Of those participants with a lifetime history of MDD, 48% also had a lifetime history of an anxiety disorder (defined as a diagnosis of GAD at ages 18, 21, 26, and 32 or as a juvenile diagnosis of overanxious disorder, separation anxiety disorder, or phobias at ages 11, 13, and 15 because GAD was not diagnosed prior to age 18 in this sample). Among individuals with a lifetime anxiety disorder (again defined as a diagnosis of GAD at ages 18, 21, 26, and 32 or as a juvenile diagnosis of overanxious disorder, separation anxiety disorder, or phobias at ages 11, 13, and 15), 72% had a lifetime diagnosis of MDD. This was done because GAD cannot be diagnosed before age 18. However, by including phobias, this may well be an overestimate of comorbidity with GAD per se. Furthermore, these patterns of comorbidity were similar in both men and women (an issue rarely examined in most studies on this topic). Together, these findings suggest that MDD and GAD frequently both occur during an individual's lifetime.

Sequential Comorbidity

Evidence of elevated cross-sectional and cumulative (lifetime) comorbidity between MDD and GAD (as well as other anxiety disorders) has prompted researchers to investigate whether one disorder is more likely to precede the other (e.g., Alloy, Kelly, Mineka, & Clements, 1990). For example, does GAD generally have its onset first, followed by MDD? Or does MDD tend to predate the onset of GAD? *Sequential comorbidity* refers to the degree to which one disorder is reliably followed by the onset of another disorder (Moffitt, Harrington, et al., 2007). Information on sequential comorbidity can not only help to inform understanding of etiology but also has potential implications for intervention and prevention. For example, if one disorder is found to be followed by another disorder at higher levels than what would be expected by chance, then treating the first disorder might have the potential to prevent onsets of the second disorder, although only if the first disorder somehow plays a causal role for (or serves as an important vulnerability factor for) the second disorder.

For many years, it was generally believed that GAD (and the other anxiety disorders) was much more likely to precede a diagnosis of MDD than MDD was likely to precede a subsequent diagnosis of GAD (e.g., Mennin et al., 2008). However, this conclusion was based mostly on studies that had only examined whether a history of GAD predicted subsequent MDD; very few studies on sequential comorbidity had considered whether a history of MDD also predicted later GAD (Moffitt, Harrington, et al., 2007). Findings from more recent studies that assessed the sequential comorbidity of MDD and GAD in a more balanced way have actually provided support for a more bidirectional sequential relationship. For example, in the Dunedin study, 37% of cases of MDD diagnosed between ages 11 and 32 were associated with prior or concurrent diagnoses of GAD or juvenile anxiety (Moffitt, Harrington, et al., 2007). An additional 10% of the MDD cases experienced onsets of GAD or juvenile anxiety after the onset of MDD. Among those individuals with a diagnosis of GAD or a juvenile anxiety disorder made between the ages of 11 to 32, a total of 32% had an onset of MDD prior to or concurrent with the onset of the anxiety disorder and an additional 41% had an onset of MDD after the onset of the anxiety disorder. In sum, the percentage of cases of MDD that were preceded by GAD (37%) was comparable to the percentage of cases of GAD that were preceded by MDD (32%). Furthermore, at least 63% of cases of MDD were not preceded by either GAD or juvenile anxiety. These findings demonstrate that MDD can predate GAD.

Further support for bidirectional sequential comorbidity between MDD and GAD was observed in the NCS and NCS follow-up assessment, which occurred approximately 10 years later (Kessler et al., 2008). Participants with a lifetime diagnosis of MDD at the NCS baseline assessment had an increased risk of experiencing a first onset of GAD over the years leading up to the NCS follow-up as compared with those without MDD (OR = 2.7), perhaps reflecting their shared genetic risk (see section 4 below). Furthermore, a baseline diagnosis of lifetime GAD also predicted the first onset of MDD over the follow-up period (OR = 3.2). Even though both relationships were statistically significant, the predictive relationship between GAD and subsequent first onset of MDD was slightly stronger than the predictive relationship between MDD and subsequent first onset of GAD (although no test of the statistical significance of this difference was reported). In addition, the magnitude of these predictive relationships decreased as the amount of time between the onsets of the initial and subsequent disorders increased. In other words, although still elevated, the risk of experiencing a subsequent first onset of either MDD or GAD became attenuated as more time passed since the onset of the initial disorder (either GAD or MDD, respectively). Nevertheless, lifetime diagnoses of MDD and GAD at baseline were still significant predictors of the first onset of both GAD and MDD, respectively, for up to a decade or more after the onset of the initial disorder.

In addition to predicting the first onsets of MDD and GAD, Kessler et al. (2008) examined prediction of the persistence of MDD and GAD over the follow-up period. In these analyses, prior GAD was found to predict the persistence of MDD, but prior MDD was not a significant predictor of the persistence of GAD. Together, these findings suggest that GAD may be a somewhat stronger predictor of subsequent first onset and persistence of MDD than MDD is of subsequent GAD onset and persistence. Nevertheless, prior MDD has been found to significantly increase vulnerability to developing GAD later on. Although this may in part reflect their common genetic diathesis, the different relative strengths of their predictive relationships (i.e., GAD preceding MDD or vice versa) cannot be explained simply by their shared genetic relationship.

Further research is needed to better understand what accounts for these patterns of sequential comorbidity. Some researchers have posited that unremitting symptoms of an initial anxiety disorder may serve as a stressor that then precipitates the onset of subsequent depression (e.g., Akiskal, 1990; Alloy et al., 1990). For example, individuals with GAD who perceive their worry to be uncontrollable might experience chronic feelings of helplessness that, after sufficient time, might contribute to feelings of hopelessness (e.g., Alloy et al., 1990). This sense of hopelessness might then put individuals at risk for developing depression. Based on this theory, it would be predicted that the longer and/or more severe the course of GAD, the greater the risk of developing subsequent depression. Longitudinal, prospective research designs that assess the duration and severity of GAD at multiple points in time and track subsequent onsets of MDD would be needed to fully address this issue. It is also of interest for future research to investigate what might account for the observed patterns of bidirectional sequential

comorbidity. In addition to sequential comorbidity being explained by the effects of one disorder on another, researchers have posited that these observed patterns might also be due to unmeasured common causes of MDD and GAD. As we discuss below, both some common genetic and environmental causes of MDD and GAD have been the subject of research (e.g., Kendler et al., 2007), and more work on this topic is clearly needed.

Etiological Models of Comorbidity Between MDD and GAD

As mentioned above, common causes of MDD and GAD have been posited as one explanation for the high rates of comorbidity between these two disorders. Indeed, models positing common causes are not unique to the co-occurrence of MDD and GAD but rather have been explored within the context of a variety of clinical presentations (e.g., associations between personality and depression) (Klein, Durbin, & Shankman, 2009). According to this model, two clinical manifestations originate from the same or at least an overlapping set of causal processes.

Over the past few decades, researchers in pursuit of common causes of MDD and GAD have explored the extent to which common genetic and/or environmental risk factors might account for the high rates of MDD and GAD co-occurrence (e.g., Kendler, Neale, Kessler, Heath, & Eaves, 1992). In this research, genetic vulnerability has been estimated with a genetic correlation, namely the extent to which the same genes increase risk for both disorders. With respect to common environmental factors, two kinds of environmental influences have generally been distinguished: (1) those that are shared by members within the same family (familial/shared environmental factors, such as socioeconomic status) and (2) those that are unique to individuals and not shared by all family members (nonfamilial/individual-specific environmental factors, such as the breakup of a romantic relationship). Genetically informative samples, such as twin studies, can help to identify the degree to which all three of these factors (genetic, familial/shared environment, nonfamilial/individual-specific environment) contribute to comorbidity between two disorders.

Genetic Contributions to Comorbidity

To date, a number of twin studies have examined genetic contributions to the comorbidity between MDD and GAD (e.g., Kendler, 1996; Kendler et al., 1992, 2007; Roy, Neale, Pedersen, Mathé, & Kendler, 1995). The results have been quite consistent across investigations in suggesting that shared genetic vulnerability primarily accounts for the co-occurrence of MDD and GAD in these twin samples. Indeed, the genetic correlations between MDD and GAD (both in terms of lifetime and past-year diagnoses) generally have been estimated to be unity (i.e., 1.0) (Kendler, 1996; Kendler et al., 1992; Roy et al., 1995). The one exception is a study by Kendler et al. (2007) in which the genetic correlation between lifetime MDD and lifetime GAD was estimated to be 1.00 for female twins but only .74 for male twins. In summary, vulnerability to MDD and vulnerability to GAD are influenced largely by the same genetic factors, although possibly slightly less so for men.

Environmental Contributions to Comorbidity

Perhaps not surprisingly, in contrast to the findings of very high genetic similarity, there has been much less evidence of sizable overlap in the environmental contributions to MDD and GAD in twin studies. For example, as for most disorders, there has been little support for a role for familial/shared environmental factors in contributing to risk for MDD or GAD. Furthermore, there has been evidence of more modest overlap between the nonfamilial/individual-specific environmental risk factors for MDD and GAD, with most estimates of the nonfamilial/individual-specific environmental correlation between MDD and GAD ranging between .2 and .6 (Kendler, 1996; Kendler et al., 1992, 2007; Roy et al., 1995). These findings suggest that although there is some overlap in the nonfamilial/individual-specific environmental risk factors for MDD and GAD, they are not entirely overlapping. Together, the results of these twin studies indicate that MDD and GAD are characterized by a highly similar (if not identical) genetic substrate, leading to the high likelihood that environmental influences primarily determine whether individuals develop MDD and/or GAD.

Neuroticism as a Common Genetic Vulnerability?

In light of these findings, researchers have been interested in identifying what may underlie this shared genetic diathesis as well as which environmental factors may contribute to the development

of MDD versus GAD. One proposed candidate for the common genetic vulnerability has been neuroticism, a broad personality trait with substantial heritability that is thought to reflect emotional instability, proneness to negative affect, and distress (e.g., Kendler, Neale, Kessler, Heath, & Eaves, 1993). Neuroticism is a strong predictor of both MDD and GAD (e.g., Moffitt, Caspi, et al., 2007), and there is evidence of genetic correlations between neuroticism and each of these disorders as well (e.g., Hettema, Neale, Myers, Prescott, & Kendler, 2006). Furthermore, a personality trait that reflects individual differences in experiencing general distress is a particularly promising candidate given that in structural models, MDD and GAD have both been found to load strongly on a general distress factor (e.g., Krueger & Markon, 2006; Watson, 2005).

To date, at least two studies have examined the degree to which the genetic factors underlying neuroticism account for the genetic correlation between MDD and GAD. In the population-based Virginia Adult Twin Study of Psychiatric and Substance Use Disorders, neuroticism was measured with the short form of the Eysenck Personality Questionnaire, and lifetime diagnoses of MDD and GAD were assigned using diagnostic interviews (Hettema et al., 2006). Consistent with prior research, there was almost complete overlap in the genetic factors associated with MDD and GAD (the genetic correlation between the two disorders was .98). This association was also broken down into genetic correlations that did and did not overlap with the genetic factors underlying neuroticism. In the Hettema et al. (2006) study, a substantial portion of the genetic variance underlying comorbidity between MDD and GAD was accounted for by the genetic factors associated with neuroticism (genetic correlation = .47). However, a sizable percentage of the genetic risk common to MDD and GAD was also independent of neuroticism (genetic correlation = .51).

Somewhat similar conclusions were drawn from a study of participants from the Swedish Twin Registry (Kendler et al., 2007). In this investigation, neuroticism was measured with nine items from the short form of the Eysenck Personality Inventory (EPI), and DSM-IV–based lifetime diagnoses of MDD and GAD were assigned approximately 25 years after the assessment of neuroticism. In this sample, genetic factors underlying neuroticism accounted for 23% and 25% of the genetic comorbidity between MDD and GAD in male and female twins, respectively. Thus in this study, genes associated with neuroticism were found to account for a considerably more modest proportion of the genetic overlap between MDD and GAD compared with the study of Hettema et al. (2006), where closer to 50% of the genetic correlation between MDD and GAD was shared with neuroticism.

However, it is worth noting several important methodological differences that existed between the Kendler et al. (2007) and Hettema et al. (2006) studies that may account for the apparent discrepancy in their findings. For example, Kendler et al. (2007) used a relatively uncommon measure of neuroticism (a small number of items selected from the EPI), whereas Hettema et al. (2006) used a more frequently employed neuroticism measure: the short form of the Eysenck Personality Questionnaire (EPQ; Eysenck & Eysenck, 1975). Perhaps even more important is that Kendler et al. assessed neuroticism 25 years prior to the assessment of psychopathology. In contrast, Hettema et al. (2006) measured neuroticism and lifetime history of MDD and GAD much more closely in time. Neuroticism is only moderately stable over long periods of time (one estimate from a meta-analysis by Roberts & DelVecchio [2000] was about .5). Thus Kendler et al.'s (2007) measure of neuroticism may not have accurately reflected the participants' neuroticism levels at the time of psychopathology assessment 25 years later. Nevertheless, together these results suggest that there is sizable—but certainly not complete—overlap between the genetic factors underlying neuroticism and the shared genetic risk for MDD and GAD. Thus it is of interest for future research to continue to explore candidates which will help to explain the genetic overlap between MDD and GAD.

Stressful Life Events as Determinants of MDD and/or GAD

Although a common genetic diathesis appears to characterize MDD and GAD, the results of twin studies suggest that different environmental risk factors determine whether this underlying vulnerability becomes manifested as MDD and/or GAD. One environmental factor—different types of stressful life events—has been the subject of research investigating such potential disorder-specific determinants. For example, Kendler, Hettema, Butera, Gardner, and Prescott (2003) examined the diagnostic specificity of different kinds of stressful life events within the population-based Virginia Twin Registry. Stressful life events were classified as loss events (e.g., death of a loved one), humiliation

events (e.g., rejection by a significant other), entrapment events (e.g., an event that prolongs and worsens current difficulties), or danger events (e.g., threat of potential future loss). Events were identified that were associated with pure MDD versus pure GAD episodes (although GAD episodes needed to be only two weeks in duration in order to make the duration requirement comparable to that for MDD) that had a minimum duration of two weeks (rather than 6 months). Humiliation events predicted pure MDD but not pure GAD episodes. In contrast, danger events predicted pure GAD episodes but not pure MDD episodes. Loss events were not specific to either disorder, but they did predict the onset of pure MDD to a greater degree than they did pure GAD episodes. Perhaps not surprisingly, onsets of "comorbid" episodes that were characterized by both depressive and generalized anxiety symptoms were predicted by stressful life events that, in general, were a sum of the predictors of pure MDD (loss and humiliation events) and pure GAD episodes (danger events). However, there was some evidence that entrapment events also predicted these mixed episodes. Overall, these findings support the notion that, with a common genetic diathesis, particular environmental factors (specifically different types of stressful life events), can differentially predict the extent to which individuals develop MDD or GAD. Furthermore, episodes of mixed depression-generalized anxiety symptoms were predicted by the sum of these more disorder-specific factors.

Nosological Issues Raised by the Comorbidity of MDD and GAD

The descriptive comorbidity results described above may be interpreted in different ways. For example, they might mean that our measures of these disorders merely lack discriminant validity due to overlapping symptoms that spuriously inflate the correlation between these two disorders. On the other hand, high comorbidity rates might mean that the two disorders represent a common underlying clinical syndrome. This latter claim would imply that the co-occurring disorders are best conceptualized as a single diagnostic entity and that the distinction made between them is not clinically or theoretically meaningful. Both these possibilities raise important challenges to a diagnostic classification system that categorizes these co-occurring disorders separately without accounting for their high rates of comorbidity (Watson, 2005). Therefore the high comorbidity rates between GAD and MDD discussed thus far raise important issues that question the validity of their current classification in the DSM-IV. The following section will address nosological concerns raised by the comorbidity between GAD and MDD and the implications of these concerns to their DSM classification.

Should MDD and GAD Be Reclassified Within the Same Diagnostic Category?

At the descriptive level, researchers have argued that the current diagnostic classification system assumes stronger relationships between disorders within a diagnostic category (e.g., social anxiety disorder and GAD) and weaker relationships between disorders across different categories (e.g. dysthymia and GAD) (Watson, 2005). However, this assumption seems to be violated to a certain extent by the evidence on both the cross-sectional and the sequential comorbidity between GAD and MDD reviewed above. One of the main limitations of the current classification system that may be responsible for this is that the DSM-IV is a rationally derived system wherein disorders are grouped together based on shared phenomenological features rather than empirical evidence that includes the rates of comorbidity between disorders (Watson, 2005).

One important nosological challenge is raised by the argument that MDD and GAD represent a single diagnostic entity and that the relationship between them extends beyond overlapping symptom criteria. In support of this view, Watson (2005) cited several lines of research pointing to their structural overlap beyond their phenotypic similarities. He also pointed out that the significant genetic correlation between them suggests that they result from similar etiological mechanisms (Kendler, Prescott, Myers, & Neale, 2003).

In addition, as alluded to above, factor analytic investigations of the latent structures underlying GAD and MDD diagnoses revealed that these two disorders were best represented as belonging to a new diagnostic category which Watson (2005) called "distress disorders." This category would incorporate disorders that were predominantly characterized by high levels of negative affect and negative affectivity. Distress disorders would be distinguished from the "fear disorders" category (comprising panic disorder, agoraphobia, social phobia, and specific phobia) and the "bipolar disorders" category (comprising bipolar I, bipolar II, and cyclothymia). Other structural modeling studies have also reached the conclusion that GAD should be recategorized along with the mood disorders.

For example, using data from the original National Comorbidity Survey, Krueger (1999) showed that GAD cohered with MDD and dysthymia, forming a common factor. Consistent with this, Vollebergh et al. (2001) fit a three-dimensional model to data from the Netherlands Mental Health Survery and Incidence Study (NEMESIS). This epidemiological study on DSM-III-R diagnoses found that GAD was best captured by the "mood disorders" dimension, which also contained MDD and dysthymia. In addition to this mood dimension, the investigators identified an "anxiety disorders" dimension consisting of specific phobia, agoraphobia, social phobia, and panic disorder and a third "substance use disorders" dimension with alcohol dependence and drug dependence. In further support of this view, Watson (2005) noted that symptoms of both GAD and MDD respond to similar pharmacological treatment, such as serotonin and norepinephrine reuptake inhibitors, which was interpreted as further evidence of their overlap (but see section on treatment implications of comorbidity below).

In light of the evidence regarding the overlap between GAD and MDD, the limitations of the current (DSM-IV) classification of these disorders have been at the forefront of much discussion, particularly during the development of the DSM-5. Specifically, some researchers have recommended that GAD and MDD be classified within the same diagnostic category in order to reflect their phenotypic, etiological, and structural overlap.

Should GAD and MDD Be Retained in Separate Diagnostic Categories?

Despite the evidence used by some to argue for grouping GAD and MDD into the same category, several important arguments that we tend to agree with have been raised against this view. These arguments suggest that such a decision would reflect certain assumptions which we believe are premature given current evidence (e.g., Mennin et al., 2008). First, categorizing GAD along with the mood disorders would seem to assume that GAD bears a stronger relationship to MDD than to the other anxiety disorders and that this would justify its being taken out of the anxiety disorders category. Second, it would seem to assume that the reasons justifying the recategorization of GAD do not apply to the other anxiety disorders—that is, that MDD shares a uniquely strong relationship with GAD compared with the other anxiety disorders. Third, the decision to subsume GAD into the MDD diagnosis would seem to assume that the current distinction made between them is not informative because both are driven by common pathological mechanisms and hence any distinction between them is spurious. Researchers who argue against the reclassification of GAD as a mood disorder primarily cite evidence that questions each of these three assumptions (e.g., Hettema, 2008; Mennin et al., 2008).

Co-occurrence of MDD with Other Anxiety Disorders

Mennin et al. (2008) reviewed evidence suggesting that both GAD and MDD also share complex relationships with other depressive and anxiety disorders and that these relationships would not be accounted for if GAD were recategorized with MDD. In support of this argument, they pointed out that although high rates of comorbidity exist between GAD and MDD, MDD has been found to co-occur at moderately high rates with other anxiety disorders as well. For example, Kessler, Chiu, et al. (2005) studied the relationships between MDD and several anxiety disorders using the NCS-R. They reported a tetrachoric correlation of .62 between MDD and GAD but also found moderate correlations between MDD and other anxiety disorders that were also high and statistically significant, including panic disorder (.48), agoraphobia (.52), specific phobia (.43), social phobia (.52), posttraumatic stress disorder (.50), and obsessive compulsive disorder (.42). A similar pattern of correlations ranging from .50 to .56 was also found between MDD and anxiety disorders by Slade and Watson (2006) using an epidemiological sample from the Australian National Survey of Mental Health and Well-Being. Finally, using a clinical sample, Brown et al. (2001) found rates of co-occurrence as high as 46% between MDD and panic disorder, which did not differ substantially from the 57% co-occurrence between MDD and GAD. It should be noted that these studies unfortunately did not report testing the statistical significance of difference of the correlations between MDD and the different anxiety disorders. Nonetheless, all of these findings raise an important point, which is that high comorbidity with MDD is not unique to GAD by any means but extends to other anxiety disorders as well (see also Hettema, 2008).

Co-occurrence of GAD with Other Anxiety Disorders

In discussing issues regarding the current classification of GAD as an anxiety disorder, Mennin et al. (2008) pointed out that removing the autonomic

symptoms from GAD diagnostic criteria from DSM-III-R for DSM-IV may have made it easier to differentiate GAD from the other anxiety disorders. However, GAD continues to correlate highly with fear disorders such as panic disorder (.61), agoraphobia (.58), social anxiety disorder (.62), and posttraumatic stress disorder (.63), which are almost as high as the correlation between GAD and MDD (.65) (Slade & Watson, 2006). Such findings imply that GAD may relate to other anxiety disorders in important ways that we should take into consideration before removing it from this category (see also Hettema, 2008). Therefore high rates of comorbidity alone do not seem to justify reclassifying GAD as a mood disorder.

Structural Analyses of Dimensional Symptom Measures

Another point that should be considered before making classification decisions based on comorbidity results is that, as mentioned earlier, these rates of comorbidity are influenced by the evolution of symptom criteria for MDD and GAD that has occurred across the DSM-III-R and the DSM-IV. Therefore we must be cautious in interpreting results from structural analyses that make use of diagnostic results from DSM-III-R versus DSM-IV because clearly the results from these studies are influenced by the nature of the inputs to these models. However, structural analyses of dimensional data would not be as susceptible to changing diagnostic criteria. Such early structural analyses of depression and anxiety symptoms measures revealed that these symptoms load onto three affective dimensions—high negative affect, low positive affect, and high autonomic arousal (Watson et al., 1995). These findings were the basis for the tripartite model of anxiety and depression (Clark & Watson, 1991). This model defined negative affect as a nonspecific factor common to both depression and anxiety, low positive affect as a depression-specific factor, and high autonomic arousal as unique to anxiety (although it was later found that anxious arousal related primarily to panic disorder and not to the other anxiety disorders) (Brown, Chorpita, & Barlow, 1998; Mineka et al., 1998).

Structural analyses of symptoms reveal two points relevant to the nosology of GAD and MDD. First, although both GAD and MDD share the negative affect dimension (Brown et al., 1998), this may not be a good basis on which to reclassify GAD with the mood disorders because negative affect is considered a nonspecific feature of, and risk factor for, multiple psychological disorders including other anxiety disorders (Clark, Watson, & Mineka, 1994; Weinstock & Whisman, 2006; Zinbarg, Mineka, et al., 2013). Second, the anxiety and depression-specific factors point to important ways in which GAD and MDD might differ from each other. Reduced positive affect has been implicated in MDD through multiple factor analytic studies (e.g., Watson et al., 1995). In addition, the role of reduced positive affect in MDD has been further supported through experimental studies that show reduced responsiveness and sensitivity to positive stimuli (e.g., Rottenberg, Kasch, Gross, & Gotlib, 2002). By contrast, to date GAD has not been linked with reduced positive affect. Indeed, Brown et al. (1998) found that MDD and social anxiety disorder (but not GAD) were both associated with low positive affectivity. This finding suggests that MDD might share certain important features with certain other anxiety disorders that it does not share with GAD.

Further, Brown et al. (1998) reported that GAD was negatively related to autonomic arousal, suggesting autonomic suppression in individuals with GAD. Borkovec, Alcaine, and Behar (2004) proposed that this may be because individuals with GAD engage in worry (a predominantly verbal activity) that inadvertently serves as a means to avoid more elaborate processing of emotional material. This, in turn, may serve to suppress autonomic hyperarousal, which might arise from more image-focused processing of threatening information (Borkovec, Lyonfields, Wiser, & Deihl, 1993). Consistent with this avoidance theory of worry (for a review see also Mineka, 2004), more recent neurobiological research supports the view that worry may be associated with cognitive disengagement from aversive imagery (Schienle, Schäfer, Pignanelli, & Vaitl, 2009). These findings of autonomic suppression have so far been demonstrated only in GAD. Indeed, MDD does not seem to be associated with suppressed autonomic arousal (Brown et al., 1998), thus further differentiating the two disorders.

Differences in Cognitive Correlates Associated with GAD and MDD

In addition to these overlapping but partially distinct affective dimensions of GAD and MDD, other points of difference between these two disorders involve cognitive and biological mechanisms that are at least somewhat specific to each. One of the key points of difference is with regard to biases in information processing of emotional material. Individuals

with GAD have consistently been found to direct their attention toward threatening (or other negative) information presented in the form of words (Mogg, Bradley, Williams, & Mathews, 1993) or faces depicting negative emotions (e.g., Bradley, Mogg, White, Groom, & De Bono, 1999). In GAD this bias has been found with different forms of negative stimuli (e.g., threat words, depression-related words, and angry faces), suggesting a relative nonspecificity in the bias toward negative emotional information in GAD, possibly due to the diverse content of worries that characterize this disorder (Mogg & Bradley, 2005). Importantly, this attentional bias is evident when negative stimuli are presented for brief periods of time (e.g., 300 to 1,000 ms). Also, nonconscious attentional biases toward negative stimuli have been demonstrated with stimuli presented for intervals as small as 14 ms (e.g., Bradley, Mogg, Millar, & White, 1995).

Nevertheless, studies have also found that when the stimulus duration is increased to allow more elaborative processing of the information (over 1,000 ms stimulus duration), individuals with GAD fail to show this attentional bias (e.g., Gotlib, Krasnoperova, Yue, & Joormann, 2004; Mogg, Millar, & Bradley, 2000). This suggests that GAD is associated with an attentional bias that occurs only at a very early stage of processing, which is not as consistently found when more elaborative processing occurs. By contrast, a different pattern of attentional bias is found in individuals with MDD such that these individuals show an attentional bias toward negative information, but only when the stimuli are presented for a longer duration of 1,000 ms or more (e.g., Gotlib et al., 2004). These findings then suggest that GAD (but not MDD) is associated with an automatic attentional bias when initially orienting to negative environmental information. In contrast, MDD (but not GAD) seems to be associated with biased elaborative processing of negative information, making it difficult for these individuals to disengage attention from negative information (for a review see Mogg & Bradley, 2005).

Furthermore, differences have also been found in terms of memory biases for negative information. Whereas MDD has been fairly consistently associated with both explicit and implicit memory biases for negative information (e.g., Rinck & Becker, 2005), the bias in explicit memory (involving conscious, effortful recall) has not been found consistently in individuals with GAD (Coles & Heimberg, 2002; for reviews, see also Mineka, Rafaeli & Yovel, 2003; Mitte, 2008). On the other hand, individuals with GAD have sometimes been found to show *implicit* memory biases toward threatening information, reflecting the unconscious influence of previously presented information (e.g., Coles, Turk, & Heimberg, 2007). However, a meta-analysis by Mitte (2008) of many such studies of implicit memory biases found no overall effect across studies. Additionally, individuals with MDD have consistently been found to show a bias toward recalling overly general autobiographical memories when asked to recall specific memories to a positive or negative cue word (Park, Goodyear, & Teasdale, 2002; Williams et al., 2007). To date, however, this bias has not been found in individuals with GAD (Burke & Mathews, 1992; Williams et al., 2007), although these authors did not use the Autobiographical Memory Test, which is the standard test used in the vast majority of research on overly general autobiographical memory in depression. Unfortunately very little research has yet addressed this question; therefore any conclusions regarding overly general memory and GAD would be premature.

Other cognitive processes that have been discussed in the context of GAD and MDD are two related forms of repetitive thinking. MDD is thought to be associated with rumination, which is a form of repetitive and passive focus on one's depressive symptoms and negative affect (Nolen-Hoeksema, 1991). Worry, on the other hand, is one of the core features of GAD and is a form of repetitive thinking focused primarily on the possibility of future negative outcomes (Borkovec, Robinson, Pruzinsky, & DePree, 1983). Research suggests substantial overlap between the processes of rumination and worry. Specifically, the self-report measures of rumination and worry tend to be highly correlated (e.g., Fresco, Frankel, Mennin, Turk, & Heimberg, 2002; Muris, Roelofs, Meesters, & Boomsma, 2004). Moreover, both rumination and worry may represent forms of unconstructive repetitive thinking that is abstract, negative, and self-focused (Watkins, 2008). Both have been associated with symptoms of depression and of anxiety (e.g., Segerstrom, Tsao, Alden, & Craske, 2000) and with negative outcomes such as poor social problem solving and inadequate solution implementation (e.g., Davey, 1994; Watkins & Moulds, 2005).

However, there are differences between worry and rumination. Factor analyses of self-report measures of rumination and worry indicate that the two constructs form separate factors (although they are correlated about .46), suggesting that they may be

statistically distinguishable (Fresco et al., 2002). As already noted, they are also thought to differ based on the content of repetitive thought, with worry being focused on future negative outcomes and rumination involving repetitive focus on past negative events and the causes and meaning of these events. Furthermore, at least based on self-report, researchers have suggested that worry and rumination may serve different functions for the individual. When ruminating, individuals report that this helps them gain better insight into their problems. On the other hand, people who engage in worrying believe that it helps them to anticipate and prepare for future threat in the face of uncertainty (for a review see Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008). In addition, as mentioned earlier, Borkovec et al. (2004) suggested that worry serves to dampen autonomic arousal and thereby permits nonconscious avoidance of aversive images and negative affect. Consequently worry prevents individuals from experiencing the likely increase in autonomic arousal that would follow from confronting such negative stimuli. Furthermore, rumination has been associated with experiencing higher levels of negative imagery compared with thoughts (McLaughlin, Borkovec, & Sibrava, 2007). In contrast, worry has been associated with higher levels of negative thought compared to imagery. Another cognitive process thought to be unique to GAD is intolerance of uncertainty, which is defined as a characteristic difficulty with ambiguous and uncertain outcomes (e.g., Dugas, Buhr, & Ladouceur, 2004). Although MDD has not been associated with especially high intolerance of uncertainty, individuals with MDD do seem to have higher certainty that negative events will occur than do individuals with GAD (Miranda & Mennin, 2007).

Are There Differences in the Neurobiological Correlates of GAD and MDD?

With respect to neurobiological correlates, some studies have found differences between GAD and MDD. As one example, GAD and MDD are thought to differ with regard to the functioning of the hypothalamic-pituitary-adrenal (HPA) axis. A number of studies have shown that MDD is associated with several aspects of HPA axis dysregulation (e.g., Goodyer, Park, & Herbert, 2001; Vreeburg et al., 2009). However, several studies have failed to find evidence of such abnormalities in individuals with GAD (Hoehn-Saric, McLeod, Lee, & Zimmerli, 1991; Pomara, Willoughby, Sidtis, Cooper, & Greenblatt, 2005). More research is clearly required to definitively conclude whether GAD is associated with HPA axis dysregulation. Furthermore, much more research is required to test the specificity of other neurobiological correlates of MDD by comparing groups that have pure diagnoses of MDD and GAD. However, space prohibits our covering other known or suspected differences here.

Are There Different Etiological Pathways for MDD and GAD?

As discussed earlier, another important point that has been used as an argument for grouping GAD and MDD together is the high degree of genetic overlap between them. Nevertheless, Hettema (2008) reviewed evidence showing that genetic overlap is not unique to MDD and GAD. For example, Lieb, Isensee, Hofler, Pfister, and Wittchen (2002) studied rates of illness in children of depressed parents, controlling for comorbid conditions in the parent. Parental MDD was significantly related to elevated rates of GAD in the offspring. However, parental MDD was also significantly associated with elevated rates in their offspring of panic disorder, obsessive compulsive disorder, and posttraumatic stress disorder. Twin studies also indicate that panic disorder shares a strong genetic relationship with GAD (e.g., Scherrer et al., 2000).

Moreover, other studies indicate that there is only a modest overlap in environmental causal factors for GAD and MDD (Kendler, Neale, et al., 1992). As reviewed earlier, studies examining stressors that precede onsets of MDD and GAD have found that different types of stressors may be linked to the development of each of these disorders (e.g., Kendler, Hettema, et al., 2003). Furthermore, along the lines of tracing etiological pathways leading to GAD and MDD, Beesdo, Pine, Lieb, and Wittchen (2010) studied developmental features associated with these two disorders. In this 10-year prospective longitudinal study, participants were between the ages of 14 and 24 at baseline and between the ages of 21 and 34 years at the last published follow-up. This investigation examined the incidence, comorbidity, and risk patterns for GAD in relation to depressive (MDD, dysthymia) and other anxiety disorders (specific phobia, social phobia, agoraphobia, and panic disorder). These analyses revealed higher hazard ratios for GAD predicting other anxiety disorders (4.14) and for other anxiety disorders predicting GAD (5.05) as compared with the association of GAD with depressive disorders (2.25). Further, the authors compared putative

risk factors for GAD to those found to be specific to two groups—those with depression alone and those with other anxiety disorders alone (without depression or GAD). These analyses revealed that factors associated with GAD overlapped with all the specific risk factors implicated in other anxiety disorders. However, GAD shared only one specific risk factor (i.e., history of parental depression) in common with depression. Thus the authors concluded that in terms of developmental features and risk factors, GAD overlapped more closely with the other anxiety disorders than with the depressive disorders.

Are Different Outcomes Associated with GAD and MDD?

Points of difference between GAD and MDD have also been found in terms of outcomes such as the course of illness and response to treatment (Hettema, 2008). Studies show that the two disorders often have somewhat different courses of illness. For example, Bruce et al. (2005) found that GAD, like the other anxiety disorders, had a more chronic course compared with MDD, with a probability of recovery (.58) at 12-year follow-up similar to that of several other anxiety disorders (e.g., recovery rates for panic disorder and social phobia were .48 and .37, respectively) On the other hand, being an episodic disorder, MDD had a somewhat higher rate of recovery (.73) than GAD.

Also, although there is some overlap in response to pharmacological treatments for MDD and GAD, this overlap is only partial. Whereas both disorders tend to respond to most antidepressants, this is not the case for anxiolytic medications, which are mostly effective for GAD but not MDD (e.g., Hettema, 2008; Levine, Cole, Chengappa, & Gershon, 2001). Furthermore, antidepressant medications have been found to be efficacious not only for GAD but also for other anxiety disorders (e.g., Ravindran & Stein, 2010). This suggests once again that the overlap with MDD is not unique to GAD alone.

Implications of These Nosological Issues

In summary, despite the different aspects of overlap between GAD and MDD, evidence suggests that both MDD and GAD relate to other anxiety disorders in important ways that must also be taken into consideration before making reclassification decisions. Further, the points of difference between MDD and GAD also suggest that the current distinction between them in the DSM-IV may be valid and informative. Such evidence has likely played a role in discussions surrounding revisions to the diagnostic criteria for GAD in DSM-5. The current proposal for diagnosing GAD in the next version of the DSM continues to list GAD as an anxiety disorder rather than as a mood disorder. However, the DSM-5 Task Force did recommend some changes in the diagnostic criteria for GAD. For example, one recommendation was to reduce the duration of anxiety and worry from at least six months to at least three months. This proposed change was based on findings that a lower duration threshold (e.g., one to five months) identifies individuals with similar symptom severity and impairment as the current six-month minimum duration requirement in DSM-IV (e.g., Kessler, Brandenburg, et al., 2005).

The DSM-5 proposed criteria for GAD also included changes to the somatic symptoms that are required for diagnosis. At present, three or more of six symptoms are required in order to receive a DSM-IV-based diagnosis of GAD. However, the new scheme in DSM-5 would have required at least one of only two symptoms: (1) restlessness, or feeling keyed up or on edge, and (2) muscle tension (Andrews et al., 2010), which are most uniquely characteristic of GAD. Although these proposed changes were approved by the DSM-5 Task Force, the American Psychiatric Association's Board of Trustees ultimately vetoed these changes and stated that they were in need of further study before being implemented.

Effects of Comorbidity

As discussed above, studies indicate that MDD and GAD may differ in terms of several cognitive correlates. Given their high rates of comorbidity, it is important to discuss the implications of co-occurring MDD and GAD on these correlates which, as discussed above, have so far largely been linked to each disorder separately. This can be accomplished by comparing comorbid individuals with those who have pure diagnoses of GAD or MDD to see whether correlates linked with one disorder manifest differently when an individual also has a comorbid diagnosis of the other. Most research on MDD and GAD has viewed comorbidity in comparison groups as a limitation that hinders the ability to draw conclusions about each disorder separately. Therefore these studies rarely draw conclusions that focus on the implications of comorbidity. However, some studies (particularly in the area of cognitive biases) have discussed findings using this perspective by viewing comorbidity not as a methodological hindrance but as having meaningful mechanistic

and theoretical significance—a perspective that we think will be likely to make important contributions to understanding these issues.

Effects of Comorbidity on Cognitive Biases

As discussed earlier, an important point discussed by Mogg and Bradley (2005) relates to the observation that whereas GAD has been extensively associated with early attentional biases for negative stimuli, this finding has not generally been found in individuals with MDD (particularly for shorter stimulus durations of less than 1,000 ms). This in spite of the fact that in several studies, most individuals in the MDD groups also have co-occurring GAD and/or show elevations in anxiety scores, comparable to levels in the pure GAD group (e.g., Bradley et al., 1995). Moreover studies that have directly compared a GAD/MDD comorbid group with a pure GAD group have found early attentional biases toward threat information in the GAD group but failed to find these biases in the comorbid group (e.g., Bradley et al., 1995; Mogg et al., 2000).

These observations imply that certain depressive mechanisms that are at play in co-occurring MDD seem to somehow mask the attentional bias seen in individuals with pure GAD. Attempting one possible explanation for these findings, Mogg and Bradley (2005) articulated a cognitive-motivational analysis of anxiety. According to this model, individuals with GAD are thought to interpret a wide range of minor environmental cues as being threatening, which in turn prompts goal engagement mechanisms that direct processing resources to these "threatening" cues. However, although individuals with comorbid MDD might similarly overestimate the threat value of environmental stimuli, their co-occurring depression may lead to relatively unresponsive goal engagement processes so that less attention is directed toward external negative cues unless the stimuli have high motivational salience for the individual (such as a high degree of self-relevance). Therefore, according to this explanation, reduced responsiveness of goal engagement processes may be responsible for the general lack of findings of early attentional biases toward negative information among individuals with co-occurring depression.

The findings discussed above suggest that researchers should look more closely at the implications of comorbid diagnoses. Obviously, however, there is a need for more studies designed especially to investigate the differences in cognitive biases in comorbid versus pure manifestations of GAD and MDD. Particularly, although most studies to date have included only two groups—pure GAD and a comorbid group (owing to the high rates of GAD diagnoses in individuals with depression)—more studies need to include three groups: one with comorbidity, one with pure GAD, and another with pure MDD. This would better allow researchers to disentangle the mechanisms at play in individual versus comorbid diagnoses.

Oehlberg, Revelle, and Mineka (2012) proposed another useful approach for studying attentional biases, taking into account the relationships between anxiety and depression. They pointed out that most studies have adopted a "disorder model" of studying attentional biases, in which different types of biases are associated with observed anxiety or depression. This approach has presupposed that each emotional disorder may be associated with a different pattern of processing emotional information. On the other hand, it could also be useful to study how attentional biases map onto underlying common and specific dimensions of anxiety and depression that have been identified by structural analyses of their symptoms. Such an approach would allow us to test whether biases are associated with negative affect (general factor model) or the specific factors associated with each disorder (specificity model).

In line with this approach, Oehlberg et al. (2012) found that early attentional biases toward angry faces at a stimulus duration of 300 ms were associated with a general tendency toward negative affectivity rather than being specifically associated with symptoms of anxiety or dysphoria per se. Further, anxious and depressive symptoms were associated with different patterns of responding to sad faces at a stimulus duration of 1,000-ms. Depressive symptoms were associated with an attentional bias toward the sad faces, and anxious symptoms were associated with a bias *away* from sad faces. However, both these latter two effects were only observed when the effects of both anxious as well as depressive symptoms were considered together in the analyses. The authors interpreted these results to suggest that the common negative affect factor primarily accounted for attentional biases toward threatening stimuli at 300 ms. However, it was the specific dimensions of anxiety and depression that accounted for their differential patterns of responding to sad stimuli at longer stimulus durations, but this effect was uncovered only when controlling for the overlapping variance between anxiety and depression.

Similarly, with regard to GAD and MDD, it may be useful to move beyond DSM-defined diagnoses

and focus instead on core symptom dimensions that are common or unique to the two disorders. By this approach, we may be able to disentangle what specific and nonspecific symptom dimensions drive attentional biases within individuals with comorbid GAD and MDD as well as study the interactive influence of each of these dimensions. These effects would not be evident if one were to conduct only group comparisons using individuals with comorbid GAD and MDD.

Effects of Comorbidity on Other Cognitive Variables

With regard to repetitive thinking, most studies indicate that pure GAD has been associated with increased levels of worry and pure MDD with increased levels of rumination. However, those with a comorbid diagnosis of both show elevations in both forms of repetitive thought, with levels of worry comparable to elevations seen in pure diagnoses of GAD and rumination levels comparable to those with pure MDD (e.g., Chelminski & Zimmerman, 2003; Hofmann, Schulz, Heering, Muench, & Bufka, 2010; Yook, Kim, Suh, & Lee, 2010). Studies have also compared levels of intolerance of uncertainty in comorbid individuals with those in persons with GAD or MDD alone. Unfortunately research on this topic has been inconsistent. For example, Yook et al. (2010) and Depuy and Ladouceur (2008) both found that individuals with comorbid GAD and MDD had higher levels of intolerance of uncertainty than those who were diagnosed with pure GAD or MDD. On the other hand, Aldao, Mennin, Linardatos, and Fresco (2010) reported similar levels of intolerance of uncertainty in those with pure and comorbid diagnoses of GAD. Therefore more research is needed to determine the implication of comorbidity for levels of intolerance of uncertainty.

Another approach through which to investigate the implications of comorbidity is to look at the biological correlates of these cognitive variables. For example, Hofmann et al. (2010) found that among individuals with GAD who were engaged in a worry task, those who had MDD had greater high-frequency heart rate variability during the worry task compared with those without depression, suggesting that depression may moderate the effects of worrying on physiological arousal. This finding provides some very preliminary evidence that different physiological correlates may underlie the cognitive manifestations of comorbid GAD and MDD as compared with a pure diagnosis of either one.

Implications of Comorbidity for Impairment

Current debates regarding the nosology of GAD and MDD have leaned toward retaining their separate classifications in the DSM-5 as well as retaining GAD in the anxiety disorder category. However, it is still important to acknowledge the impact of high comorbidity rates between these two disorders. Given that each disorder alone is associated with significant impairment, it is not surprising that comorbidity would be associated with a higher degree of impairment and cost compared with the unique diagnosis of either alone. For example, Hunt, Slade, and Andrews (2004) found that among individuals with GAD, comorbidity with MDD had implications for higher levels of disability than comorbidity with other anxiety disorders. In addition, Carroll, Phillips, Gale, and Batty (2010) reported findings from the Vietnam Experience Study suggesting that when the presence of GAD, the presence of MDD, and the comorbid occurrence of GAD and MDD were included as predictors in a fully adjusted model predicting the incidence of hypertension, only comorbidity emerged as a significant predictor. In terms of the cost implications, findings suggest that the comorbid diagnosis of MDD in individuals with GAD is linked with higher annual inpatient costs, total annual costs, and a higher likelihood of being hospitalized than is the case for individuals with a diagnosis of pure GAD (Zhu, Zhao, Ye, Marciniak, & Swindle, 2009). These findings point to the clinical significance of the comorbidity between GAD and MDD and the need to take comorbidity into consideration in treating these disorders.

Treatment Implications of Comorbidity

Given the high degree of impairment and severity associated with the co-occurrence of MDD and GAD, an important point to consider is the psychotherapeutic treatment implications of this comorbidity. That is, to what extent should a comorbid diagnosis of either GAD or MDD be taken into consideration in treating either of these disorders? Treatment studies suggest that cognitive behavioral treatments targeting one disorder are only sometimes effective in also reducing symptoms and maintaining gains with regard to the comorbid diagnosis. For example, Newman, Przeworski, Fisher, and Borkovec (2010) found that 14 weekly sessions of cognitive behavioral therapy targeting GAD reduced co-occurring MDD symptoms immediately after treatment. Unfortunately these gains for MDD symptoms were not retained at

follow-up. In fact, the clinical severity ratings for MDD at a 24-month follow-up were no longer significantly different from pretreatment levels. Nevertheless, these findings are perhaps not surprising given the high rates of relapse and recurrence observed in depression and the challenges that they pose for treatment of the disorder (e.g., Richards & Perri, 2010).

Given the high rates of comorbidity and the implications of this comorbidity for treatment outcomes, it is important to study and implement specific strategies in the clinical setting that may be useful with comorbid cases. Belzer and Schneier (2004) made several clinical recommendations for addressing co-occurring depression and anxiety that may still be useful to consider in the specific context of GAD and MDD. Specifically, it is important that individuals presenting with one of the disorders be evaluated for co-occurring symptoms of the other, even if they occur at subsyndromal levels, because this may impact treatment response. It would also be useful to obtain a longitudinal perspective on symptom manifestation by determining the age of onset and temporal course of each set of symptoms. For example, anxiolytic medication might be more beneficial in cases where a mild depressive episode occurs within the context of high levels of chronic worry compared with patients who experience increased worry primarily during a depressive episode. Therefore it is important to tailor treatment to an individual, taking into account the diverse profiles of MDD and GAD symptoms with which individuals present.

As mentioned in an earlier section, SSRIs are known to be helpful in treating symptoms of both anxiety and depression. Such medication may be useful in treating individuals with comorbid GAD and MDD. However, more research is needed to determine the efficacy of specific SSRIs in treating individuals with comorbidity. Also, the efficacy of an SSRI in reducing co-occurring anxiety symptoms may differ across different anxiety disorders given that the efficacy of SSRIs varies across anxiety disorders (for a more detailed account on issues with medication treatment of anxiety and depression see Belzer & Scheier, 2004).

One useful approach in treatment may be to reduce pathological processes that are common to GAD and MDD. One such approach is metacognitive therapy, rooted in the metacognitive model of emotional disorders (Wells & Matthews, 1996). According to this model, individuals who are prone to engage in maladaptive repetitive thinking in response to negative thoughts and emotions believe that such forms of thinking are useful in solving their problems. They also tend to carry negative beliefs that their thoughts and emotions are uncontrollable and carry great significance.

Metacognitive therapy aims to reduce repetitive thinking in the form of rumination in depression and worry in GAD by (1) building awareness of these negative forms of repetitive thought, (2) challenging positive metacognitive beliefs about the usefulness of such forms of thinking, and (3) challenging negative metacognitive beliefs about the uncontrollability and significance of negative thoughts and feelings. Some research suggests that this approach may be effective in treating individuals with GAD (Wells & King, 2006) and MDD (Wells et al., 2009). However, more research is needed to determine its efficacy in treating individuals with co-occurring GAD and MDD.

Unified Protocols for Treating Comorbid Depression and Anxiety

Along similar lines, some researchers have proposed a unified treatment approach specifically for the purpose of treating multiple diagnoses of mood and anxiety disorders. Such an approach would make use of the fact that these two classes of disorders share certain underlying vulnerabilities and expressions of pathological emotional responding. For example, given that high negative affect is a nonspecific characteristic of most emotional disorders (including GAD and MDD), addressing core processes that lead to increased levels of negative affect may be a useful strategy in treating individuals with co-occurring anxiety and depression. Other nonspecific targets for therapeutic change would include altering biases in cognitive processing that are shared by co-occurring disorders (e.g., overestimating the probability of negative outcomes) and reducing behavioral avoidance that may arise out of attempts to reduce or avoid negative affect. For example, Moses and Barlow (2006) proposed a unified approach that would begin with psychoeducation about the nature and function of emotions and emotional distortions and continue by focusing on three main aspects: modifying antecedent cognitive appraisals, changing behaviors or "action tendencies" that occur in response to emotional states, and, finally, preventing emotional avoidance.

Testing the preliminary efficacy of such a treatment plan based on such a unified protocol, Ellard, Fairholme, Boisseau, Farchione, and Barlow (2010) presented results from two open clinical trials using

a heterogeneous clinical sample of participants with multiple anxiety and depressive diagnoses. They demonstrated that the unified protocol was effective in treating both the principal diagnosis of an anxiety disorder (including GAD) and also in reducing symptoms of the comorbid diagnosis (which included MDD) both at posttreatment and at six-month follow-up. Additional initial empirical support for the unified protocol as a transdiagnostic treatment for anxiety disorders and co-occurring MDD was obtained in at least one study to date by Farchione et al. (2012). These investigators demonstrated the efficacy of this treatment in comparison to wait list controls in achieving subclinical responder or high end-state functioning status in individuals with co-occurring MDD or dysthymia. Nevertheless, it will be very important to replicate such findings using more rigorous control conditions, particularly because the number of individuals with GAD and co-occuring depression was quite small in this study.

Another integrative approach that is more behavioral was also proposed by Weersing, Gonzalez, Campo, and Lucas (2008) for treating comorbid depression and anxiety in a youth population. Their "graded engagement" technique integrates behavioral activation techniques for depression and exposure techniques for anxiety. Therefore, given the commonalities in the vulnerability towards and mechanisms underlying GAD and MDD, such unified approaches to treatment could be very beneficial with individuals with comorbid GAD and MDD. However, much more research is required to test the extent of the efficacy (and effectiveness) of unified treatment protocols specifically in treating individuals with comorbid GAD and MDD.

Conclusions

In conclusion, this chapter has reviewed many of the major findings and controversies that have emerged in the past 25 years since DSM-III-R (1987) regarding the comorbidity of GAD and MDD. GAD is certainly not the only anxiety disorder to have high comorbidity with MDD. However, among the different anxiety disorder/MDD comorbidities, the GAD/MDD comorbidity topic has been perhaps the most controversial, given that the DSM-5 Task Force was charged with evaluating the evidence regarding whether GAD should actually be removed from the anxiety disorder category and placed in the unipolar mood disorder category. Our review has led us to conclude that they should remain in separate categories, as they have been. Clearly, however, more research on this topic is warranted, and the DSM-5 Task Force seems to have come to the same conclusion. We briefly discussed the known genetic overlap between GAD and MDD but also the relative paucity of our knowledge at this point regarding the different environmental precursors of GAD versus MDD. We also reviewed the effects on cognitive biases and on impairment of having comorbid GAD and MDD. Finally, we discussed the clinical implications of comorbid GAD and MDD and approaches that may be useful in addressing this comorbidity in a clinical setting.

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CHAPTER

10 Depression and Alcohol Use

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Abstract

The World Health Organization (WHO) has identified alcohol and depression as the third and fourth largest risk factors for disease burden and leading causes of disability. Co-occurring alcohol-use disorder and depression has been linked to a more severe course of illness and worse treatment outcomes. In this chapter, we review the literature on alcohol use, depression, and their comorbidity. In addition to prevalence data we review common risk and protective factors that may impact comorbid alcohol-use disorder and depression, specifically focusing on individual differences and the environment including social and family factors, personality, cognitive, and other psychiatric factors, as well as genetic and neurobiological factors. Assessment and treatment approaches as well as clinical considerations for working with clients who have depression and co-occurring alcohol-use disorders are addressed.

Key Words: alcohol abuse, alcohol dependence, depression, negative affect, alcohol relapse, alcohol craving

Introduction

Harmful alcohol use and depression are global public health problems, impacting millions of individuals worldwide and significantly contributing to the global burden of disease. The World Health Organization (WHO) has identified alcohol use as the world's third largest risk factor for disease burden and as a leading risk factor for premature mortality and disability in the Americas and Europe (WHO, 2011a). Likewise, the WHO has identified depression as the world's fourth largest risk factor for disease burden and a leading cause of disability (WHO, 2011bb). Importantly, harmful alcohol use and depression commonly co-occur (Grant & Harford, 1995), and both alcohol use and depressed mood have been shown to be influential risk factors for the development of depressive and alcohol-use disorders, respectively (Boden & Fergusson, 2011; Conner, Pinquart, & Gamble, 2009). In this chapter, we review the literature on alcohol use and depression, including: prevalence data, etiology and common risk and protective factors, assessment and treatment issues, and clinical considerations for working with clients who have depression and co-occurring alcohol use or alcohol-use disorders.

Prevalence and Impact

Alcohol

Approximately 55% of the world's population has consumed alcohol and 11.5% of drinkers report weekly heavy drinking (more than two drinks) occasions (WHO, 2011a). In the United States in 2010, 54.1% of individuals reported having at least one drink and 15% reported binge drinking (five or more drinks for men and four or more for women) in the past 30 days (Centers for Disease Control and Prevention, 2011). Based on the most recent population in the United States of 308 million, these numbers reflect that approximately 46 million individuals in the United States engage in binge drinking at least once per month.

Alcohol use can be characterized on a continuum from no use (i.e., abstention) to nonharmful use (i.e., moderate drinking) to harmful use (i.e., binge drinking, without disorder) to alcohol-use disorder. The text revision of the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)*, by the American Psychiatric Association (APA), distinguishes two types of alcohol-use disorder: alcohol abuse and alcohol dependence (see symptoms of both disorders in Table 10.1). Both disorders are characterized by "a maladaptive pattern of drinking, leading to clinically

Table 10.1 Symptoms for Alcohol Abuse and Dependence from the DSM-IV-TR and ICD-10

DSM-IV-TR **Alcohol abuse (1+ over 12 months)**	**Alcohol dependence (3+ over 12 months)**	ICD-10 **Harmful use (all criteria at least 1 month, or repeated for 12 months)**	**Alcohol dependence (3+ at least 1 month, or repeated for 12 months)**
Recurrent use of alcohol resulting in a failure to fulfill major role obligations at work, school, or home.	Need for increased amounts of alcohol to achieve desired effect; or markedly diminished effect with continued use of the same amount of alcohol.	Clear evidence that alcohol use contributed to physical or psychological harm, which may lead to disability/adverse consequences.	Need for significantly increased amounts of alcohol to achieve desired effect; or markedly diminished effect with continued use of the same amount of alcohol.
Recurrent alcohol use in situations in which it is physically hazardous.	Withdrawal or drinking to relieve or avoid withdrawal symptoms.	The nature of harm should be clearly identifiable (and specified).	Withdrawal or drinking to relieve or avoid withdrawal symptoms.
Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol.	Persistent desire or one or more unsuccessful efforts to cut down or control drinking.	Symptoms do not meet criteria for any other mental or behavioral disorder related to alcohol in the same time period (except for acute intoxication).	Difficulties in controlling drinking in terms of onset, termination, or levels of use; drinking in larger amounts or over a longer period than intended; or a persistent desire or unsuccessful efforts to reduce or control drinking.
Recurrent alcohol–related legal problems.	Drinking in larger amounts or over a longer period than intended.		Important pleasures or interests given up or reduced because of drinking. OR
	Important social, occupational, or recreational activities given up or reduced because of drinking.		A great deal of time spent in activities necessary to obtain, to use, or to recover from the effects of drinking.
	A great deal of time spent in activities necessary to obtain, to use, or to recover from the effects of drinking.		Persisting with drinking despite clear evidence and knowledge of harmful physical or psychological consequences.
	Continued drinking despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to be caused or exacerbated by drinking.		A strong desire or sense of compulsion to drink.

Note. Diagnostic criteria from the DSM-IV-TR (APA, 2000) and International Classification of Diseases—10 (WHO, 1992),

significant impairment or distress" occurring over a 12-month period (APA, 2000). The 10th edition of the *International Classification of Diseases* (ICD-10, 1992), by the WHO, distinguishes alcohol dependence from harmful alcohol use (see Table 10.1). In both the *DSM* and the *ICD*, a diagnosis of alcohol dependence supersedes an abuse diagnosis when criteria for both disorders are met. The fifth edition of the *DSM* (*DSM-5*) and the 11th edition of the *ICD* (*ICD-11*) are currently under development, and the most recent proposals for *DSM-5* recommend combining the symptoms of abuse and dependence into a single disorder, called alcohol-use disorder (http://www.dsm5.org, last accessed 12/29/2011).

Alcohol-use disorder is one of the most common substance-use disorders. The worldwide prevalence of alcohol-use disorder in 2004 was roughly 3% (WHO, 2011a). Results from the 2001–2002 National Epidemiological Survey on Alcohol and Related Conditions (NESARC) in the United States indicated that the lifetime and past-year prevalence of alcohol abuse was 17.8% and 4.7%, respectively, whereas the lifetime and past-year prevalence of alcohol dependence was 12.5% and 3.8%, respectively. Based on the 2001–2002 population in the United States of 286 million, these numbers reflect that approximately 54 million and 24 million individuals in the United States met criteria for an alcohol-use disorder (alcohol abuse or dependence) in their lifetime and past year, respectively (Grant et al., 2006; Hasin, Stinson, Ogburn, & Grant, 2007).

Depression

Depression is the most common single mental disorder (anxiety disorders are the most common group of disorders), affecting approximately 121 million individuals worldwide. Among adults in the United States, the past-year prevalence of major depressive disorder was 6.7% and the past-year prevalence of dysthymia was 1.5% (Kessler, Chiu, Demler, & Walters, 2005). Among 13- to 18-year-olds the lifetime prevalence of major depressive disorder or dysthymia was 11.2% (Kessler, Chiu, et al., 2005). According to 2010 data from the United States Behavioral Risk Factor Surveillance System, approximately 28% of those surveyed reported feeling "down, depressed, or hopeless" in the past two weeks, and 18% reported being told they had a depressive disorder by a doctor or other health-care provider.

Alcohol use and depression

As noted earlier, depression and alcohol-use disorders commonly co-occur. Results from the first United States National Comorbidity Survey (NCS) indicated 21% past year and 40% lifetime prevalence of major depression among those with alcohol abuse or dependence (Grant & Harford, 1995). The prevalence of comorbid depression and alcohol-use disorder was especially high among males (35% past year, 55% lifetime) and among 18- to 29-year olds (30% past year, 46% lifetime). Similarly, data from the 2008 National Survey on Drug Use and Health (Substance Abuse and Mental Health Services Administration, 2011) indicated that 16.7% of individuals who reported having a major depressive episode in the past year also met criteria for an alcohol-use disorder, whereas only 6.7% of individuals who did not report a major depressive episode in the past year met criteria for an alcohol-use disorder. Thus, the number of individuals meeting criteria for alcohol abuse or dependence was 2.5 times greater among those with a major depressive episode in the past year.

A longitudinal investigation of subthreshold and full-syndrome psychiatric disorders in a community sample of young adults from ages 16 to 30 found that 35.3% of individuals who had subthreshold depression symptoms at the first assessment met full criteria for depression at some point in the future (Shankman et al., 2009). Among those with subthreshold alcohol problems at the first assessment, 36.4% met full criteria for an alcohol-use disorder in the future. The rates of comorbidity of alcohol disorder and depression were 11.1% and 13.5% for full scale and subthreshold criteria, respectively, at the first time point. Among those who met full or subthreshold criteria for depression at the first time point, 31.1% and 20.8%, respectively, met full criteria for an alcohol-use disorder at a later time point, and among those who met full or subthreshold criteria for an alcohol-use disorder at the first time point, 41.7% and 30.2%, respectively, met full criteria for depression at a later time point. Thus, symptoms of depression and symptoms of alcohol-use disorder portend increased risk for developing alcohol-use and depression disorders in the future.

Morbidity and mortality

As noted earlier, both alcohol-use disorders and depression increase risk for disability and mortality (WHO, 2011a, 2011b). Among neuropsychiatric disorders, unipolar depression and alcohol use were responsible for the greatest burden of disease measured in disability-adjusted life years (DALYs), which provide an estimate of the total number of years lost to illness, disability, or premature death.

A recent analysis of the disease burden in Europe found that unipolar depression and alcohol use were the first and third largest contributor to total disease burden, respectively (Wittchen et al., 2011). Alcohol-use disorders have been shown to greatly increase risk of gastrointestinal diseases (e.g., liver cirrhosis and pancreatitis), certain forms of cancer (Baan et al., 2007), cardiovascular disease (Rehm, 2011), diabetes (Baliunas et al., 2009), infectious diseases (Lönnroth, Williams, Stadlin, Jaramillo, & Dye, 2008), and both intentional and unintentional injury. Depression has been shown to be a risk factor for cardiovascular disease (Celano & Huffman, 2011), diabetes (Knol, Twisk, Beekman, Heine, Snoek, & Pouwer, 2006), stroke (Pan, Sun, Okereke, Rexrode, & Hu, 2011), cancer (Satin, Linden, & Phillips, 2009), pulmonary disease (Schane, Walter, Dinno, Covinksy, & Woodruff, 2008), and both intentional and unintentional injury (Patten, Williams, Lavorato, & Eliasziw, 2010). Moreover, both alcohol and depression have been associated with increased functional impairment, poor medication and self-care adherence, and greater medical costs (see Katon, 2011; WHO, 2011a).

Fewer studies have systematically examined the morbidity and mortality of comorbid depression and alcohol-use disorder, although the available data would suggest a higher mortality risk associated with comorbid alcohol use and depression than either disorder independently. Using data from the United States National Alcohol Survey and National Death Index, Greenfield, Rehm, & Rogers (2002) found that, among those with higher levels of depression, males who engaged in daily heavy drinking (more than six drinks per day) and females who were former drinkers with heavy drinking occasions had a fourfold and threefold mortality risk, respectively, in comparison to lifetime abstainers from alcohol. When compared to lifetime abstainers who were not depressed, both males and females who were depressed heavy drinkers had greater than four times the risk of mortality. Male and female heavy drinkers who were not depressed did not have an increased risk of mortality. The authors concluded that depression may amplify the negative health effects of heavy drinking (Greenfield et al., 2002). In addition, numerous studies have identified alcohol use and alcohol-use disorder as risk factors for attempted and completed suicide among individuals with depression (e.g., Bossarte & Swahn, 2011; Conner, Beautrais, & Conwell, 2003; Galaif, Sussman, Newcomb, & Locke, 2007; Schneider, 2009; Sher et al., 2005).

Etiology and Common Risk/Protective Factors

Numerous etiologic models have been proposed for both alcohol-use disorders and depression, with most research pointing to a complex interplay between genetics, individual differences (including neurobiological, emotional, behavioral, personality, and temperament factors), and the environment (Cicchetti & Cohen, 2006; Kendler, Aggen, Prescott, Crabbe, & Neale, 2012; Mueser, Drake, & Wallach, 1998). Importantly, many studies have found a significant degree of heterogeneity in the development, symptom presentation, and progression of both alcohol-use disorders and depression, which is a major impediment to understanding how depression and alcohol use develop independently and how they come to co-occur.

Numerous etiologic models of alcohol-use disorders have received strong empirical support, and it has been acknowledged that multiple pathways may lead to the development of alcohol problems (Sher & Slutske, 2003). The most relevant etiologic model of alcohol-use disorders for the purposes of understanding the etiology of comorbid depression and alcohol-use disorders is the negative-affect-regulation model (see Sher, Grekin, et al., 2005 for a review of additional models). The negative-affect-regulation model maintains that alcohol problems develop because of an individual's expectation that alcohol relieves negative-affective states (including stress, depressed mood, and anxiety). As noted by Goldman, Brown, and Christiansen (1987) "If any characteristic has been seen as a central, defining aspect of alcohol use, it is the presumed capacity of alcohol to alter anxiety, depression, and other moods" (p. 200). Among social drinkers, alcohol use has been shown to correlate with activation of pleasure circuitry in the brain and can also attenuate anxiety (Gilman, Ramchandani, Davis, Bjork, & Hommer, 2008). Yet, alcohol is a central nervous depressant, and there is considerable evidence that drinking to relieve negative affect predicts greater elevations in negative affect in subsequent weeks (Hussong, Hicks, Levy & Curran, 2001). Also, drinking to cope with negative affect increases rates of consumption and alcohol-related problems (e.g., Cooper, Russell, & George, 1988; Kassel, Jackson, & Unrod, 2000). Thus, although many individuals with alcohol-use disorders hold an expectation that alcohol can help alleviate negative affect, there is considerably greater evidence that alcohol might actually exacerbate negative affective states and that

drinking to cope with negative affect can lead to greater consequences associated with alcohol use.

The negative affect regulation model of alcohol-use disorder implies that negative affect should precede the onset of alcohol-use disorder. Indeed, recent research has attempted to delineate whether there is a causal relation between depression and alcohol-use disorder, but the findings are mixed (Boden & Fergusson, 2011; Deas & Thomas, 2002; Kuo, Gardner, Kendler, & Prescott, 2006). Developmental psychopathology research and data from twin studies has found that depression tends to precede alcohol-use disorder (e.g., Kaplow, Curran, Angold, & Costello, 2001), whereas registry-based research has found that alcohol-use disorders tend to be clinically identified before mood disorders (Flensborg-Madsen, Mortensen, Knop, Becker, Sher & Grønbæk, 2009). Boden and Fergusson (2011) conducted a narrative review and meta-analysis of 16 epidemiological studies that have examined comorbid depression and alcohol-use disorders. The results from the meta-analysis indicated that having either depression or an alcohol-use disorder doubled the risk of having the other disorder, and there was not a clear finding of directionality. In the narrative review, the authors suggested that there is more evidence that alcohol involvement *causes* depression, but this suggestion was based on only one prior study (Fergusson, Boden, & Horwood, 2009). The author's suggestion that alcohol involvement causes depression has been challenged in the literature (Conner, 2011; Flensborg-Madsen, 2011). A meta-analysis of 74 studies found that depression symptoms predicted future alcohol involvement and impairment, as well as earlier age of onset of alcohol-use disorder (Conner et al., 2009). Similarly, a study of 2,603 monozygotic twins found that major depression substantially increased the risk of developing alcohol dependence, whereas an earlier onset of alcohol dependence did not have a significant effect on the future development of major depression (Kuo et al., 2006).

An important consideration and potential explanation for the discrepancy across studies is the reliance on measures of lifetime or past-year diagnosis, with less consideration of symptom overlap or temporal precedence. Recent research has identified important differences in the presentation of "primary" depression (i.e., depression that occurs independent from alcohol-use disorder), as compared to "secondary" or "substance-induced" depression (i.e., depression that only occurs during periods of or immediately following heavy alcohol use). For example, numerous studies have found that individuals with primary depression are more often female (Grant, Hasin & Dawson, 1996; Schuckit et al., 1997; Schuckit et al., 2007), tend to be more severe with higher levels of dysfunction (Kahler, Ramsey, Read, & Brown, 2002; Schuckit et al., 1997; 2007), and often have higher levels of depression symptoms (Cohn et al., 2011), than individuals with secondary depression. Unfortunately, the majority of research studies of comorbid depression and alcohol-use disorder have not made a distinction between primary and secondary depression. Given this lack of distinction, the current review is focused on the shared risk and protective factors in the development of comorbid alcohol use and depression, with only a few references to primary and secondary depression.

Demographic risk factors

Numerous studies have found that males are at greater risk for an earlier onset of alcohol use and are more likely to develop an alcohol-use disorder (e.g., Hasin et al., 2007), whereas females are at much greater risk for depression (Kessler, Berglund, Demier, Jin, & Walters, 2005). Interestingly the data are mixed about whether the prevalence of comorbid alcohol-use disorder and depression varies by gender. In a recent U.S. Survey (the NESARC), males and females had a near-equal prevalence of comorbid alcohol and depression (Cranford, Nolen-Hoeksema, & Zucker, 2011). In older U.S. surveys (National Longitudinal Alcohol Epidemiologic Survey and National Comorbidity Survey), the association between depression and alcohol-use disorders was higher among females (Grant & Harford, 1995; Kessler et al., 1997). In contrast, results from the Netherlands Study of Depression and Anxiety indicated that males were at greater risk for comorbid depression and alcohol dependence (Boschloo et al., 2011). In the Great Smoky Mountain Study, the association between depression and alcohol use was significant among males only (Costello, Erkanli, Federman, & Angold, 1999). Mason, Hawkins, Kosterman, and Catalona, (2010) found that being male significantly increased the odds of developing comorbid alcohol-use disorder and depression by age 21. Similarly, Sher and colleagues (2008) found that male gender predicted a history of comorbid alcohol-use disorder among depressed patients.

Ethnic and racial differences in the prevalence of comorbid depression and alcohol-use disorders have also been identified, and results are also mixed.

Cranford and colleagues (2011) found that rates of comorbid alcohol-use disorder and depression were highest among American Indians and lowest among Asians, whereas Huang and colleagues (2006) found that comorbid alcohol-use disorder and depression was most common among African Americans, Asian Americans, and Hispanics, in comparison to Caucasians. Among a treatment-seeking sample of individuals with alcohol dependence, the rates of comorbid depression were highest among Alaska Natives and Caucasian patients, in comparison to African American and Hispanic patients (Hesselbrock, Hesselbrock, Segal, Schuckit, & Bucholz, 2003). Among adolescents, Maag and Irvin (2005) found that African American adolescents had an increased probability of concomitant symptoms of depression and heavy alcohol use.

Only a few studies have examined differences in the rates of comorbidity among urban and rural residents. Simmons and Havens (2007) found that individuals in rural areas with past-month major depression were significantly more likely to meet past-month criteria for an alcohol-use disorder, in comparison to urban residents. Among a veteran population in the United States, both alcohol dependence and major depression were more prevalent among urban residents in comparison to rural residents, although the authors did not report on the prevalence rates for comorbid alcohol-use disorder and depression (Weeks, Wallace, Wang, Lee, & Kazis, 2006).

Socioeconomic status and education levels have also been examined in a few studies. Low income has been shown to be a significant risk factor for both lifetime and past-12-month comorbid alcohol-use disorder and depression (Wang & El-Guebaly, 2004). In a longitudinal study conducted in New Zealand, Poulton and colleagues (2002) found that low socioeconomic status during childhood was predictive of alcohol dependence at age 26, and both depression and alcohol dependence at age 26 were significantly associated with adult socioeconomic status. Lower levels of education have also been associated with alcohol-use disorders (Crum, Helzer, & Anthony, 1993; Hasin et al., 2007; Swendsen et al., 2009), depression, and comorbid depression (Blazer, Kessler, McGonagle, & Swartz, 1994).

In summary, low socioeconomic status and low income are the only sociodemographic risk factors that have been consistently found to be associated with an increased risk for comorbid depression and alcohol disorders. Gender, ethnicity/race, and urbanicity have all been found to predict comorbid depression and alcohol-use disorders, but the nature of the associations have varied across studies.

Family and social environment factors

Numerous family and social factors have been found to be either risk or protective factors for the development of comorbid alcohol-use disorders and depression. Family history of alcohol-use disorders has been found to be a robust predictor of comorbid alcohol-use disorder and major depression (e.g., Dawson & Grant, 1998; Sher et al., 2008). Parental depression has also been found to predict greater risk of depression and alcohol dependence among the children of depressed parents (Weissman, Warner, Wickramaratne, Moreau, & Olfson, 1997). Fewer studies have examined the familial transmission of comorbid alcohol-use disorder and depression. Twin studies have found that familial risk is transmitted within disorder, but comorbid alcohol-use disorder and depression does not appear to have an increased familial liability (Kuo et al., 2006; Prescott, Aggen, & Kendler, 2000) and one recent study found that the small degree of familial association between alcohol-use disorder and depression was fully explained by mood-related drinking motives (Young-Wolff, Kendler, Sintov, & Prescott, 2009). Thus, family history of comorbid depression and alcohol-use disorder might increase risk of comorbid depression and alcohol-use disorder, but there is not strong support for a genetic risk of comorbid transmission.

Adverse family environment during childhood and particularly a history of child abuse has been shown to predict comorbid depression and alcohol-use disorder (e.g., De Bernardo, Newcomb, Toth, Richey, & Mendoza, 2002; Sher et al., 2008). In one study, adverse childhood experiences, defined as emotional, physical, or sexual abuse, witnessing domestic violence, parental separation or divorce, and living with drug-abusing, mentally ill, or criminal household members, were found to have a graded association between alcohol-use disorder and depression in adulthood (Anda et al., 2002). Clark, De Bellis, Lynch, Cornelius, and Martin (2003) conducted a longitudinal study to examine the association between physical and/or sexual abuse and comorbid alcohol use and depression in a sample of individuals who were initially recruited in adolescence and followed through young adulthood. Results indicated that physical and/or sexual abuse was strongly associated with

primary depression and significantly accelerated the onset of primary depression, secondary depression, and comorbid alcohol-use disorders.

Adverse living situation and violence may also impact comorbid depression and alcohol-use disorder in adults. Numerous studies have found a strong association between homelessness and depression and alcohol symptoms (e.g., Nyamathi, Keenan, & Bayley, 1998; Rodell, Benda, & Rodell, 2001; Smith, North, & Spitznagel, 1993). Marital status, specifically being unmarried, has also been associated with comorbid major depression and alcohol-use disorders (Boschloo et al., 2011; Wang & El-Guebaly, 2004). Among individuals with an alcohol-use disorder, violence victimization has been shown to predict more depressive symptoms, as compared to those with alcohol-use disorders who were not victimized (Schneider, Timko, Moos, & Moos, 2011). Intimate partner violence has also been associated with greater alcohol use and depression symptoms (Lipsky, Caetano, Field, & Bazargan, 2005; Schneider, Burnette, Ilgen, & Timko, 2009). Thus, childhood and adulthood living environment and exposure to abuse or violence are associated with greater risk of comorbid alcohol-use disorder and depression.

Family environment and early childhood experiences can also serve as protective factors. Recently, Mason, Hawkis, Kosterman, and Catalona (2010) conducted a longitudinal study of social and developmental predictors of co-occurring alcohol and depression in young adulthood (age 21) among a community sample of children who were assessed annually from ages 10 to 21. Controlling for adolescent (age 13) anxiety and depression symptoms, as well as alcohol or other drug problems, the authors found that adolescent (age 14) family cohesion, parental rewards for good behavior, rewarding school experiences, and bonding to school and family were significantly associated with a lower risk of comorbid alcohol-use disorders and depression at 21 years of age, in comparison to experiencing an alcohol-use disorder (without comorbid depression) or experiencing depression (without a comorbid alcohol-use disorder). Importantly, school and family factors were more predictive of the occurrence of comorbid alcohol-use disorder and depression in young adulthood than were the presence of anxiety or depression symptoms assessed at age 13, whereas alcohol or other drug problems at age 13 did significantly predict the occurrence of comorbid alcohol-use disorder and depression at age 21.

Personality, cognitive, and other psychiatric risk factors

Individual differences in personality, cognitions, and other psychiatric comorbidity have been shown to be among the strongest predictors of comorbid alcohol-use disorder and depression. Sher and colleagues (2008) found that aggression, impulsivity, hostility, behavior problems during childhood and tobacco smoking each significantly predicted alcohol-use disorder among depressed patients. In multivariate analyses the authors found that aggression and tobacco smoking were the strongest predictors of comorbid alcohol-use disorder and depression (Sher et al., 2007). Boschloo and colleagues (2011) also found that tobacco smoking (former or current) and lack of conscientiousness (e.g., impulsivity) were significantly associated with comorbid alcohol dependence among individuals with a lifetime depressive disorder. Liu, Chiu, and Yang (2010) also found that patients with comorbid alcohol dependence and depression had higher impulsivity scores than patients with alcohol dependence who did not have comorbid depression. Childhood externalizing problems (e.g., conduct disorder and oppositional defiant disorder), more generally, have been found to predict concurrent depression and heavy alcohol use or alcohol abuse (King, Ghaziuddin, McGovern, & Brand, 1996; Windle & Davies, 1999) and may moderate the association between depression and the development of alcohol-use disorder (see Hussong, Jones, Stein, Baucom, & Boeding, 2011 for a review of plausible mechanisms).

Cognitive factors, including expectancies, motives, and self-efficacy, have also been identified as salient for the comorbidity of depression and alcohol-use disorder. As noted earlier, negative-mood-regulation expectancies have been associated with the development of comorbid depression and alcohol dependence (Young-Wolff et al., 2009) and drinking to cope with negative emotions has been found to mediate the association between depression symptoms and implicit evaluation of alcohol (Ralston & Palfai, 2011). Drink-refusal self-efficacy, or one's belief in their ability to refuse alcoholic drinks, was found to be significantly lower during depressed mood induction among college student drinkers (Ralston & Palfai, 2010) and general self-efficacy has been shown to mediate the association between alcohol dependence and depression (Sitharthan, Hough, Sitharthan, & Kavanagh, 2001). Similarly, Mason and colleagues (2010) found that greater drink

refusal self-Ed, SRefficacy was associated with a significantly lower likelihood of comorbid depression and alcohol-use disorder.

In addition to personality and cognitive factors, numerous studies have found that alcohol and depression commonly co-occur with additional psychiatric disorders. In the National Comorbidity Survey-Replication study, Kessler, Berglund, et al. (2005) found the 12-month prevalence of meeting criteria for three or more disorders was 6% (23% of those with any disorder had three or more). Anxiety disorders (Boschloo et al., 2011), nicotine and other drug dependence (Compton, Thomas, Stinson, & Grant, 2007), posttraumatic stress disorder (Karlović, Solter, Katinić, & Potkonjak, 2004), borderline personality disorder (Eaton et al., 2011), antisocial personality disorder (Fu et al., 2002), and schizophrenia (Scheller-Gilkey, Thomas, Woolwine, & Miller, 2002) have all been identified as commonly co-occurring with comorbid depression and alcohol-use disorders. Numerous recent studies have attempted to delineate latent factors that explain common variance in the structure of comorbidity among psychiatric disorders (Cosgrove et al., 2011; Kessler et al., 2011; Kotov et al., 2011) with the majority of studies focusing on internalizing (including depression) and externalizing (including alcohol-use disorder) factors. Across studies, the latent internalizing and latent externalizing factors are distinct, but highly correlated, with shared genetic and environment influences predicting their comorbidity. Yet recent longitudinal analyses have found that alcohol-use disorders are less likely to share a significant amount of variance with an externalizing factor (Vrieze, Perlman, Krueger, Iacono, 2011), and it has been hypothesized that alcohol-use disorder may be more strongly associated with internalizing psychopathology over time (Hussong et al., 2011; Kushner et al., 2012). Future research should examine whether specific psychiatric disorders are more or less likely to precede the development of comorbid depression and alcohol-use disorder.

Genetic factors

Twin studies have provided evidence that depression and alcohol-use disorder are genetically correlated (Kendler, Neale, Kessler, Heath, & Eves, 1993; Lyons et al., 2006; Prescott, Aggen, & Kendler, 2000), with some evidence for sex-specific genetic and environmental risk (Prescott et al., 2000). Specifically, Prescott and colleagues (2000) found that genetic factors explained more of the covariance between major depression and alcohol dependence in males (61%) than females (51%), whereas environmental factors explained more covariance in females (49%) than males (39%). Approximately 9–14% of the covariance between depression and alcohol dependence was explained by shared genetic and environmental factors (Prescott et al., 2000). Nurnberger and colleagues (2001) identified a region linked to both alcohol dependence and depression on chromosome 1 and numerous single-gene studies have found support for specific genes that are associated with both depression and alcohol-use disorders, such as dopamine receptor D2 (*DRD2*; Dick et al., 2007), cholinergic muscarinic receptor 2 (*CHRM2*; Wang et al., 2004), and serotonin transporter gene subtypes (see Saraceno, Munaf, Heron, Craddock, & Van den Bree, 2009 for a review). A genome-wide linkage scan for major depression found no regions of interest that reached genome-wide significance in a sample of sibling pairs with alcohol dependence (Kuo et al., 2010). Similarly, a recent genome-wide association study of comorbid depression and alcohol dependence found that no single nucleotide polymorphism met genome- wide significance criteria, and there was only modest overlap in significant polymorphisms between the comorbid group and the alcohol-dependence-only group (Edwards et al., 2012). There were numerous limitations to both genome-wide studies that may have reduced the likelihood of identifying specific regions of interest or single nucleotide polymorphism. It is also the case that heterogeneity in the comorbid phenotype could further dilute the findings. For example, Schuckit and colleagues (2007) found different etiologies for primary versus secondary depression, yet an individual with secondary depression (i.e., alcohol-induced depression) and an individual with depression independent from substance use disorder would appear to have the same comorbid phenotype.

Research on gene-gene interactions and gene-environment interactions has become particularly important in understanding the etiology of comorbid depression and alcohol-use disorder. With respect to gene-gene interaction, a study of 427 Chinese men found that anxiety, depression, or mixed anxiety and depression comorbid with alcohol dependence was 3.45 times more likely among those carrying the 3-repeat allele of the monoamine oxidase type A gene (*MAOA*) and the A1/A1 genotype of the *DRD2* gene, as compared to those carrying the *MAOA* 3-repeat allele and the A2/A2 genotype of the *DRD2* gene (Huang et al., 2007). With respect to gene-environment interaction,

Sjöholm and colleagues (2010) examined genetic variation among 1,039 individuals selected from the Finish Health 2000 study, specifically selecting single-nucleotide polymorphisms that have been previously associated with substance use or mental-health disorders. The authors were particularly interested in whether genetic variation in the circadian clock system was associated with comorbid depression and alcohol-use disorder. The sample included 76 individuals with comorbid depression or dysthymia and an alcohol-use disorder, 446 individuals with alcohol-use disorder only, and 517 sex and age-matched controls who had no psychiatric symptoms. Results indicated that the circadian clock homolog gene (*CLOCK*) was associated with comorbid depression and alcohol-use disorder (odds ratio = 1.65), but was unrelated to alcohol-use disorder only. A prior study found that the *CLOCK* gene was not associated with major depression or dysthymia (Utge et al., 2010), thus it seems that the *CLOCK* variation observed by Sjöholm and colleagues (2010) could be a genetic vulnerability factor for depression that is influenced by environmental alcohol exposure. It is important to note that given the temporal precedence of depression preceding alcohol use in numerous studies (e.g., Conner et al., 2009; Kaplow et al., 2001; Kuo et al., 2006), the gene-environment interaction identified by Sjöholm and colleagues (2010) would only explain depression that is secondary to alcohol exposure and would not explain primary depression that precedes the initiation of alcohol use. Distinguishing between primary and secondary depression phenotypes may help clarify genetic influences in future gene-environment interaction studies.

Neurobiological factors

Major depressive disorders and alcohol-use disorders share common neurobiological dysfunction (Brady & Sinha, 2005). Drawing from a neurobiological framework Brady and Sinha (2005) proposed three potential explanations for the comorbidity between depression and alcohol-use disorders. First, it could be the case that chronic alcohol use causes neuroadaptations that produce the biological abnormalities observed in major depressive disorders (Markou, Kosten, & Koob, 1998). This "neuroadaptation hypothesis" requires chronic alcohol use to precede the depressive symptomatology, which is inconsistent with some of the literature reviewed earlier. Second, it could be the case that alcohol and depression are unique symptom expressions of the same underlying neurobiological deficits and depression, alcohol-use disorder, or both could be readily expressed. A third hypothesis is that chronic distress may be a third variable explanation for the neurobiological dysfunction that is observed in both depression and alcohol-use disorders. In other words, repeated exposure to stressors facilitates a cascade of neuroadaptations in the stress and reward circuits of the brain, which may underlie the neurobiological dysfunctions seen in depression and alcohol-use disorders. This hypothesis is supported by data showing that individuals with depression, alcohol-use disorders, and comorbid depression and alcohol-use disorder often have a history of trauma (e.g., De Bernardo et al., 2002; Sher et al., 2008) and difficulties in coping with distress (see Sher et al., 2005). Importantly, the shared neurobiological deficits hypothesis and the chronic distress hypothesis do not require a temporal ordering and are more appealing for characterizing alcohol-use disorder and depression as co-occurring, rather than causally related.

Consistent with all three hypothesized explanations for comorbidity, dysfunctions in neural circuitry have been identified across depression and substance-use disorders (including alcohol), particularly in the ventromedial prefrontal cortex (vmPFC), the dorsolateral prefrontal cortex (dlPFC), the amygdala, and the insula (Brewer, Bowen, Smith, Marlatt & Potenza, 2010). Similarly, both depression and alcohol use have been associated with dysfunctions in the same neurotransmitter systems, including the mesocorticolimbic dopamine system, serotonergic systems, and cholinergic systems (for reviews see Rao, 2006; Rao & Chen, 2008). Other neurotransmitters/neuromodulators that have been implicated in both depression and alcohol-use disorders include GABA, glutamate, corticotropin-releasing hormone, and neuropeptide Y (see Alfonso-Loeches & Guerri, 2011; Carvajal, Dumont, & Quirion, 2006; Chopra, Kumar, & Kuhad, 2011). Although these data support neurobiological overlap across depression and alcohol-use disorders, few studies have empirically examined neurobiological mechanisms of co-occurring depression and alcohol-use disorders (see Kertes et al., 2011; Rao & Chen, 2008).

Prevention and Treatment Approaches

Prevention

The goal of prevention is to reduce the occurrence of a disorder or disease in a given population by identifying risk and protective factors that contribute to

the disorder and targeting those factors on a broad scale to reduce the likelihood of individuals developing the disorder (Institute of Medicine, 1990). Given many of the shared risk and protective factors for comorbid alcohol use and depression, described earlier, it follows that prevention programs could be developed to prevent the development of comorbid depression and alcohol-use disorder. Currently, numerous prevention programs exist that focus on depression (Stice, Shaw, Bohon, Marti, & Rhode, 2009; Beardslee, Gladstone & O'Connor, 2011) and there are also several alcohol abuse and dependence prevention programs (Matano et al., 2001; Gottfredson & Wilson, 2003; Hustad, Barnett, Borsari, & Jackson, 2009; Palfai, Zisserson & Saitz, 2011). Yet, no prevention programs attend to the co-occurance of depression and alcohol use or disorder. Mason and colleagues (2010) studied the effects of adolescent social-development protective factors and their outcomes at age 21 for alcohol-use disorders only, depression only, and co-occurrence. As noted earlier, the authors identified seven protective factors that predicted co-occurrence: alcohol-related refusal skills, academic skills, bonding with family, school bonding, having a rewarding school experience, parents rewarding good behavior, and family cohesion. Developing prevention programs that focus on these common protective factors could potentially contribute to a reduction of the co-occurrence of depression and alcohol-use disorders. More research on the prevention of comorbid disorders is sorely needed.

Pharmacological treatments

There are more than 25 different drugs in five drug classes that are approved by the Food and Drug Administration (FDA) for the treatment of depression. These include selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOI), tricycle antidepressants, atypical antidepressants, and select serotonin and norepinephrine reuptake inhibitors (SNRIs). More than 75% of individuals receiving outpatient treatment for depression in the United States are prescribed some form of antidepressant medication (Marcus & Olfson, 2010). On the contrary, there are only three FDA approved medications for alcohol dependence (acamprosate, naltrexone, and disulfiram) and it has been estimated that fewer than 10% of individuals with alcohol dependence receive a prescription medication (Mark, Kassed, Vandivort-Warren, Levit, & Kranzler, 2009). One study estimated that the majority of addiction treatment programs surveyed were more likely to prescribe SSRIs than FDA approved medications for alcohol dependence (Ducharme, Knudsen, & Roman, 2006).

Hobbs and colleagues (2011) conducted a meta-analysis of studies that have examined antidepressant treatment for depression among patients with alcohol dependence. The authors identified eight randomized controlled trials that examined the efficacy of supplemental depression pharmacotherapy, including five studies that examined SSRIs, two studies that used SNRIs, and one study used imipramine (a tricyclic antidepressant). The effect sizes for SSRIs on depression outcomes ranged from -0.03 to 0.40 and for SSRIs on alcohol outcomes ranged from -0.52 to 0.62. The effect of SNRIs on depression outcomes ranged from 0.36 to 0.71 and the effect of SNRIs on alcohol outcomes ranged from 0.16 to 0.64. Finally, the one study that examined the effect of imipramine found an effect of 0.34 on depression outcomes and 0.17 on alcohol outcomes (McGrath et al., 1996). The overall effect sizes for supplemental pharmacotherapy on both depression and alcohol outcomes were small (d= 0.24 for depression, d = 0.18 for alcohol). These results were consistent with an earlier meta-analysis of studies that examined supplemental depression treatment for alcohol and substance-use disorders (Nunes & Levins, 2004).

Fewer studies have examined the efficacy of treating comorbid alcohol-use disorders and depression with medications for alcohol dependence. Pettinati and colleagues (2010) found that naltrexone in combination with an SSRI (sertraline) resulted in significantly higher abstinence rates, a longer time to the first heavy drinking day, and lower depression rates after 14 weeks of treatment, than naltrexone alone, sertraline alone, or placebo in the treatment of depression and alcohol dependence. Studies of naltrexone, disulfiram, or acamprosate in the treatment of alcohol dependence among individuals with depression have found that depression symptoms are not adversely affected by the medications, there are no interactions between depression symptoms and medication in the prediction of alcohol outcomes, and that reductions in drinking, regardless of the medication, are associated with reductions in depression symptoms (Lejoyeux & Lehert, 2011; Petrakis et al., 2007).

Psychological treatments

In comparison to the high rates of prescription-medication use among depression outpatients, far fewer receive psychotherapy. Marcus

and Olfson (2010) reported that only 43% of individuals receiving outpatient treatment for depression in the United States received some form of psychotherapy. These numbers are in stark contrast to treatment utilization rates for alcohol dependence, in which the majority of patients receive some form of psychological treatment, rather than medications. Miller and Wilbourne (2002) conducted a review of 361 controlled clinical trials of treatments for alcohol-use disorders and provided a summary of the evidence of treatment effectiveness for 87 different treatments. Cognitive, behavioral, and motivational treatments were the most effective psychotherapies for alcohol dependence identified in their review. Cognitive and behavioral treatments, such as cognitive therapy, behavioral activation, and cognitive-behavior therapy, have also been widely supported as effective in the treatment of depression and other psychological treatments (e.g., interpersonal psychotherapy, mindfulness-based cognitive therapy) have also been shown to be effective (see Cuijpers, van Straten, Warmerdam, & Andersson, 2008 for a review of 149 studies).

Only a few studies have been conducted that have examined the effectiveness or efficacy of psychological treatments for comorbid alcohol-use disorder and depression (see review by Baker, Thornton, Hiles, Hides, & Lubman, 2012). Brown, Evans, Miller, Burgess, and Mueller (1997) found that cognitive-behavioral treatment for depression among alcohol dependent patients resulted in greater reductions in depressive symptoms during treatment and significantly better drinking outcomes at a six-month follow-up, compared to a relaxation control condition; however, these findings were not replicated in a subsequent study with a larger sample size (Brown et al., 2011). In a large study of co-occurring depressive symptoms and hazardous alcohol use Baker and colleagues (2009) found that an integrated cognitive behavioral treatment, which focused on both depression and alcohol use, was associated with a significant reduction in depressive symptoms and drinking days in comparison to alcohol-only focused or depression-only focused interventions. In another study by the same research group, the authors found that computer-based integrated cognitive behavioral treatment was as effective as an in-person integrated cognitive behavioral treatment for comorbid depression and alcohol and/or cannabis-use disorders (Kay-Lambkin, Baker, Lewin, & Carr, 2009).

Studies that have examined psychological treatment of comorbid substance-use disorder and depression provide additional evidence for the effectiveness of integrated treatments. In a pre-post design, Hides, Samet, and Ludman (2010) found that integrated cognitive behavioral therapy for co-occurring depression and substance misuse was associated with significant improvements in depression and substance use following treatment among 15- to 25-year-olds. Similarly, Watkins and colleagues (2011) found that an integrated group-cognitive-behavioral therapy for depressed patients in residential substance-abuse treatment resulted in significant improvements in depressive symptoms and improved mental-health functioning three months after starting treatment, as well as fewer drinking days and fewer days of problematic substance use six months after starting treatment, in comparison to a usual-care control group.

Combined treatments

Treatments that provide a combination of psychotherapy and pharmacotherapy have been found to be more effective than pharmacotherapy alone in the treatment of depression (Cuijpers, Dekker, Hollon, & Andersson, 2009) and alcohol dependence (Anton et al., 2006; Oslin et al., 2008; Weiss & Kueppenbender, 2006). As summarized in a review of dual diagnosis treatments by Kelly, Daley, and Douaihy (2012), the best outcomes for alcohol-use disorder and depression were found among combination treatments that integrated an antidepressant with psychotherapy. Farren, Snee, and McElroy (2011) found that individuals with bipolar or unipolar depression and alcohol dependence showed marked reductions in depression scores and drinking behavior up to two years following an integrated inpatient treatment that combined pharmacotherapy and psychotherapy. Brown and colleagues (2006) found that standard pharmacotherapy plus integrated cognitive behavioral treatment for comorbid depression and substance-use disorder was more effective in reducing substance use through a six-month follow-up than standard pharmacotherapy plus 12-step facilitation. Both treatments were associated with improvements in depression and substance use during treatment.

Clinical Considerations

As noted throughout this chapter, distinguishing between primary and secondary depression that co-occurs with alcohol-use disorder is an important first step in the treatment of comorbid alcohol-use disorder and depression. A thorough assessment of symptoms and symptom overlap is

critical for making an appropriate diagnosis and in the development of a treatment plan. Within an alcohol-treatment setting it is important for practitioners to screen for depression symptoms. Delgadillo and colleagues (2011) found that the nine-item, self-report, Patient Health Questionnaire (Kroenke, Spitzer, & Williams, 2001) was a reliable and valid depression-screening tool in an alcohol- and drug-treatment program. Given that depression symptoms tend to remit after a period of abstinence or reduced use (e.g., Goldsmith & Ries, 2003), it is important to conduct an assessment of depression at the initiation of treatment and after the client has made at least some progress in treatment. Within a depression treatment setting, a brief alcohol-screening device could be used to assess for the presence of potential problems related to alcohol use. For example, the three alcohol consumption items from the Alcohol Use Disorder Identification Test (AUDIT-C) is a reliable and valid screening test for heavy drinking and/or alcohol-use disorder (Bush, Kivlahan, McDonell, Fihn, & Bradley, 1998). The screening of depression in alcohol-treatment settings and screening for alcohol-use disorders in depression-treatment programs is particularly important given the low rates of treatment seeking for individuals with depression and alcohol-use disorders. For example, a client who is willing to see a therapist for help with his or her depression may have never considered seeking treatment for an alcohol problem. The therapist can provide the conduit for alcohol treatment.

The presence of both an alcohol-use disorder and depression has been associated with a more severe course of illness and worse treatment outcomes (e.g., Davis et al., 2010; Hasin et al., 2002; Sher et al., 2008). Targeting both disorders within an integrated treatment program that incorporates both psychotherapy and pharmacotherapy, as reviewed earlier, has been found to be most effective in this population (Quello, Brady, & Sonne, 2005). Yet, it may be difficult to provide an integrated treatment, particularly if one disorder is more severe than the other. Clients who are severely depressed, especially those experiencing catatonic or psychotic symptoms, may be unable to participate in an alcohol treatment program. These individuals would mostly likely benefit from a psychiatric inpatient or an intensive outpatient treatment program where alcohol use is prohibited and withdrawal symptoms can be closely monitored. Likewise, individuals who are severely dependent on alcohol and are depressed are at risk for multiple complications, such as suicide and alcohol withdrawal. These individuals would likely benefit from inpatient detoxification services prior to receiving treatment for their depression. Fortunately, there is evidence that providing treatment for one disorder can prevent or reduce symptoms associated with the other disorder (see review by O'Neil, Conner, & Kendall, 2011).

Summary and Conclusions

The occurrence of comorbid alcohol-use disorder and depression is both common and debilitating. There is considerable research on the risk and protective factors associated with the etiology of alcohol-use disorder and depression, as well as a growing literature on the risk and protective factors associated with their comorbidity. Research on the treatment of comorbid alcohol-use disorder and depression has lagged behind the epidemiological and etiological research, yet promising integrated O'ntreatment approaches have been developed and are worthy of further study. It is critical that future research take into consideration the issue of temporal sequencing and to examine possible moderating effects of primary depression versus substance-induced depression. In general, more research needs to be conducted on whether distinct comorbid phenotypes exist and whether treatments are more or less effective for different expressions of the comorbid disorders. Given that effective treatments are available, an important next step is to facilitate dissemination of effective treatments to providers and to improve the implementation of new programs that can address the complex needs of this population.

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CHAPTER

11 Eating Disorders

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Abstract

This chapter examines patterns of comorbidity between eating disorders and mood, anxiety, and substance use disorders along with evidence regarding support for different theoretical models that may account for these patterns. Although comorbidity estimates may be inflated by reliance on treatment-seeking samples and double counting of symptoms that overlap between syndromes, evidence supports elevated risk of mood, anxiety, and substance use disorders in anorexia nervosa, bulimia nervosa, and binge eating disorder. Data from family and twin studies support that eating and anxiety disorders may have a shared diathesis, consistent with the common cause model. Data from longitudinal studies suggest that eating disorders may increase vulnerability for developing a substance use disorder, consistent with the predisposition model. In contrast, comorbidity between eating and mood disorders, such as depression, remains poorly understood. Clinical issues regarding comorbidity of depression and eating disorders along with guidelines for clinicians treating patients with comorbid depression and eating disorders are discussed.

Key Words: anorexia nervosa, bulimia nervosa, binge eating disorder, depression, mood disorders, anxiety disorders, substance use disorders, comorbidity

Introduction

Eating disorders are serious and sometimes chronic mental illnesses that are associated with distress, psychosocial impairment, medical morbidity (Klump, Bulik, Kaye, Treasure, & Tyson, 2009), and increased risk of death (Arcelus, Mitchell, Wales, & Nielsen, 2011), including death by suicide (Preti, Rocchi, Sisti, Camboni, & Miotto, 2011). Both threshold and subthreshold eating disorders demonstrate high levels of comorbidity with mood disorders (Hudson, Hiripi, Pope, & Kessler, 2007; Preti et al., 2009). In addition, individuals with eating disorders are at increased risk for lifetime anxiety and substance use disorders compared with individuals without eating disorders (Hudson et al., 2007; Preti et al., 2009). Indeed, an individual who has only a lifetime diagnosis of an eating disorder represents the exception rather than the rule. High levels of comorbidity raise questions regarding the mechanisms that underlie co-occurrence. One early model of bulimia nervosa (BN), the "affective variant hypothesis" (Pope & Hudson, 1984), posits that BN represented a variant of mood disorders. Alternative models have been offered to explain high levels of comorbidity as well (Wonderlich & Mitchell, 1997). This chapter provides a brief description of eating disorders, reviews patterns of comorbidity between eating disorders and other mental disorders, describes overlapping features that might inflate comorbidity estimates, and describes theoretical relationships that could explain why eating disorders are more likely to co-occur with other psychiatric illnesses. Finally, clinical guidelines for the treatment of

individuals presenting with comorbid mood and eating disorders are discussed.

Table 11.1 summarizes lifetime prevalence rates of core disorders from the recent National Comorbidity Survey Replication (NCS-R) reported for anorexia nervosa (AN), bulimia nervosa (BN), and binge eating disorder (BED) (Hudson et al., 2007). Importantly, mood, anxiety, and substance use disorders demonstrate high levels of comorbidity with one another (Kessler et al., 2003), suggesting that eating disorders are not unique in showing co-occurrence with other mental disorders. However, there is asymmetry in comorbidity between eating and other disorders, such that the majority of individuals with an eating disorder have a comorbid mood disorder, but the majority of individuals with mood disorders do not have a comorbid eating disorder. Such patterns underscore the value of examining comorbidity in eating disorders.

Description of Eating Disorders

The fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) (APA, 1994) recognizes two specific eating disorders, AN and BN. In addition, the DSM-IV includes a residual category for eating disorders that do not meet criteria for AN or BN, referred to as eating disorder not otherwise specified (EDNOS). BED is one example of an EDNOS, and diagnostic criteria for BED were included in Appendix B of the DSM-IV. Subsequent research on BED has supported its validity (Crow et al., 2012; Keel, Brown, Holm-Denoma, & Bodell, 2011), resulting in the proposed inclusion of BED as a third specific eating disorder in the DSM-5 (www.dsm5.org). Most research on comorbidity in eating disorders has focused on these defined syndromes; the remainder of the chapter focuses on AN, BN, and BED.

AN is defined by extreme dietary restriction that results in medically low body weight, an intense fear of gaining weight or becoming fat, a perceptual body image disturbance whereby individuals perceive themselves as fat despite being clearly underweight, undue influence of weight or shape on self-evaluation, or denial of the seriousness of low body weight, and, in women, amenorrhea (APA, 1994). Proposed DSM-5 criteria will eliminate the amenorrhea criterion and the requirement for explicit endorsement of intense fear of gaining weight or becoming fat (www.dsm5.org). The DSM-IV defines two subtypes for AN, a restricting type (ANR) and binge eating/purging type (ANBP). ANR indicates an absence of binge eating or purging behavior, whereas ANBP is characterized by recurrent episodes of binge eating or purging behavior. Research supports clinically significant differences between these two subtypes. ANBP has been associated with older age, more suicidal behaviors, and more comorbid personality disorders characterized by impulsivity as compared with ANR (Peat, Mitchell, Hoek, & Wonderlich, 2009). In contrast, ANR has been associated with higher constraint and perfectionism and often resembles obsessive-compulsive personality disorder in clinical presentation (Peat et al., 2009). Of interest, longitudinal data support considerable crossover between subtypes such that individuals falling in the ANR category are likely to later develop binge eating episodes (Eddy et al., 2002, 2008), such that some of the differences observed between ANR and ANBP may reflect effects of age and chronicity. According to estimates from population-based studies, AN

Table 11.1 Lifetime Comorbidity Odds Ratios for Core DSM-IV Disorders in Eating Disorders Reported in the National Comorbidity Survey Replication and Disorders with Highest Odds Ratio for Each Eating Disorder

	Anorexia Nervosa			Bulimia Nervosa			Binge Eating Disorder		
	%	OR	95% CI	%	OR	95% CI	%	OR	95% CI
Mood disorders	42.1	**2.4**	1.2–4.7	70.7	**7.8**	3.6–16.8	46.4	**3.1**	1.9–4.8
Anxiety disorders	47.9	1.9	0.9–4.1	80.6	**8.6**	3.4–21.6	65.1	**4.3**	2.6–7.1
Substance use disorders	27.0	**3.0**	1.2–7.1	36.8	**4.6**	2.0–10.8	23.3	**2.1**	1.2–3.8
Any disorders	56.2	1.3[a]	0.6–3.1	94.5	**17.6**[b]	4.5–68.4	78.9	**4.2**[a,b]	2.2–7.9

Note: Bolded ORs are significantly greater than 1.0. ORs with different superscripts have nonoverlapping 95% confidence intervals (CIs).
Source: Adapted with permission from Hudson, J. I., Hiripi, E., Pope, H. G., & Kessler, R. C. (2007). The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication. *Biological Psychiatry, 61*(3), 348–358.

occurs in approximately 0.6% (Hudson et al., 2007) to 1.0% (Bijl, Ravelli, & van Zessen, 1998) of the general population and most commonly develops in women in late adolescence or early adulthood (Swanson et al., 2011). The sex ratio for AN has been estimated to be approximately 10:1 in women and men (Hoek & van Hoeken, 2003); however, data from more recent epidemiological studies suggest that the prevalence of AN among men is higher than reported in past studies, with an estimated lifetime prevalence of 0.3% in men compared with 0.9% in women (Hudson et al., 2007).

BN is defined by the presence of recurrent episodes of binge eating accompanied by inappropriate compensatory behaviors that have occurred, on average, twice per week over the previous three months and the undue influence of weight and shape on self-evaluation (APA, 1994). Proposed DSM-5 criteria will reduce the frequency of episodes to once per week for three months (www.dsm5.org). Binge episodes are defined by consumption of an unusually large amount of food within a limited period of time and a sense of loss of control over eating during the episode. Inappropriate compensatory behaviors include both purging (self-induced vomiting, laxative abuse, diuretic abuse) and nonpurging (excessive exercise, fasting) behaviors and are used to distinguish between the purging and nonpurging subtypes of BN in the DSM-IV (BNP and nonpurging BN, or BNnP, respectively). Previous studies have found that BNP is both more common and associated with higher levels of psychopathology than BNnP (Hay, Fairburn, & Doll, 1996). However, proposed DSM-5 criteria will eliminate the distinction between these subtypes, given the paucity of research on BNnP (www.dsm5.org). A diagnostic hierarchy exists in the DSM-IV for AN and BN, such that if an individual simultaneously meets criteria for AN and BN, a diagnosis of ANBP trumps a diagnosis of BN. According to data from the NCS-R, lifetime prevalence of BN is 1.5% among women and 0.5% among men ages 18 and older (Hudson et al., 2007), compared with 1.3% among adolescent women and 0.5% among adolescent men (Swanson et al., 2011).

BED is characterized by recurrent binge eating episodes in the absence of inappropriate compensatory behaviors. Binge eating episodes must be associated with three of five possible features, which include eating more rapidly than usual, eating until feeling uncomfortably full, eating large amounts of food when not physically hungry, eating alone owing to embarrassment over the quantity of food being consumed, and feeling disgusted with oneself, depressed, or very guilty following binge episodes (APA, 1994). In addition to intense negative affect immediately following binge episodes, the individual must endorse significant distress regarding the presence of binge eating episodes in his or her life. In the DSM-IV, binge-eating episodes must occur two days per week for at least six months; however, proposed criteria for the DSM-5 will reduce this to once per week for three months (www.dsm5.org). In addition to the absence of inappropriate compensatory behaviors, a diagnosis of BED can be given only in the absence of a diagnosis of AN and BN. According to estimates from population-based studies, BED occurs in approximately 1.1% (Preti et al., 2009) to 2.8% (Hudson et al., 2007) of the general population and most commonly develops in women in late adolescence or early adulthood (Swanson et al., 2011). The lifetime prevalence of BED is approximately three to seven times higher in women than in men (Preti et al., 2009; Swanson et al., 2011).

Patterns of Comorbidity Between Eating Disorders and Mood and Other Disorders

All eating disorders are associated with high rates of psychiatric comorbidity (Blinder, Cumella, & Sanathara, 2006; Pallister & Waller, 2008). Braun and colleagues (1994) reported that 81.9% of women with eating disorders met criteria for at least one comorbid Axis I disorder. However, substantial variation exists across studies regarding comorbidity prevalence estimates in eating disorders, likely reflecting the use of different study populations. Comorbidity estimates from treatment-seeking samples are generally higher than in population-based samples given the impact of Berkson's bias (Berkson, 1946) and may inflate estimates that are based on patients with eating disorders (McElroy et al., 2005). Further, core and associated features of AN, BN, and BED often overlap with symptoms of other disorders; thus it is possible that clinicians may count one symptom toward the diagnosis of both an eating disorder and another disorder, which may increase comorbidity estimates. In consideration of these issues, estimates of comorbidity are reviewed from the NCS-R in addition to studies of clinical eating disorder populations. The NCS-R utilizes a nationally representative population-based sample which controls for the possible influence of Berkson's bias. However, because this studied relied on lay interviewers, areas of overlap between features of eating disorders and

other psychiatric illnesses may have contributed to dual diagnoses. Thus overlap in features is described.

Mood Disorders

Studies examining comorbidity in eating disorders suggest that major depressive disorder is the most commonly observed comorbid psychiatric disorder in AN (Bulik, 2002; Hudson et al., 2007). According to the NCS-R, approximately 39.1% of women with AN report at least one major depressive episode in their lifetimes (Hudson et al., 2007). Consistent with depressive symptomatology, women with AN display weight loss, flat affect, feelings of hopelessness, social withdrawal, a sense of worthlessness and guilt, extremely low self-esteem, irritability, insomnia, and suicidal ideation and attempts (Bulik, 2002). Teasing apart whether these symptoms are due to a coexisting mood disorder or are secondary to AN can be challenging for a clinician. For instance, a major depressive episode may be associated with weight loss and/or loss of appetite. However, weight loss in depression occurs due to a loss of motivation to eat, whereas weight loss in AN reflects effortful restriction of calories allowing for differentiating these superficially similar symptoms. Determining whether a concurrent diagnosis of major depressive disorder is warranted is further complicated by the fact that many depressive symptoms (e.g., loss of energy, insomnia, decreased concentration, etc.) are secondary to starvation. Patient reports and evidence from structured clinical interviews indicates that the pattern of onset of depression can occur before or following the onset of AN (Bulik, Sullivan, Fear, & Joyce, 1997; Wade, Bulik, & Kendler, 2000), and timing of onset of eating and comorbid depression has important clinical implications, which are discussed later in this chapter. Although depressive symptoms tend to improve throughout refeeding, long-term outcome studies indicate that mood disturbances may persist even after weight recovery in AN (Bulik, 2002). Thus, in some individuals, depression may be secondary to an inadequate energy supply, whereas in others mood symptoms may be independent of AN course and a concurrent diagnosis of major depressive disorder is warranted.

In addition to major depressive disorder, dysthymia is approximately 4.5 times more common in individuals with AN than in the general population (Hudson et al., 2007). Similar to the challenges posed by symptom overlap in major depressive disorder and AN, it is difficult to determine whether biological and cognitive changes caused by starvation put individuals with AN at greater risk for developing dysthymia or whether the dysthymic symptoms justify a separate diagnosis (Borda-Más, Torres-Pérez, & Río-Sánchez, 2008).

In contrast to major depressive disorder and dysthymia, the prevalence of bipolar disorder (bipolar I–II) is not significantly elevated in AN (Hudson et al., 2007; McElroy et al., 2011), occurring in 3% of individuals with AN (Hudson et al., 2007). While mood disturbance in AN is characterized largely by dysphoric symptoms, overlap in symptoms between AN and mania has been described. For example, studies have reported that features characteristic of AN—such as restlessness associated with insomnia and overactivity (e.g., excessive exercise), mood labiality, irritability, and poor insight—may also be interpreted as symptoms of a manic episode (Casper, 1998; McElroy et al., 2005). Thus, it has been proposed that mood dysregulation and behavioral activation observed in AN could be mistaken for core features of bipolar disorder. Unfortunately the number of lifetime diagnoses of AN in the NCS-R ($N = 18$) was too small to evaluate prevalence by subtype (Hudson et al., 2007).

According to data from the NCS-R, mood disorders are approximately eight times more common in individuals with BN than in the general population, occurring in 70.7% of individuals with BN (Hudson et al., 2007). Among specific mood disorders, major depressive disorder occurs in 50.1% of individuals with BN, making it four times more common in BN than in the general population. Like AN, depression may occur both prior to and following the onset of BN, and it may persist even after bulimic symptoms are no longer present (Brewerton et al., 1995; Kaye et al., 1998). BN is associated with transient guilt, rumination, and dysphoric mood, which may trigger and increase following binge eating episodes (Haedt-Matt & Keel, 2011a). In addition, hyperphagia, a symptom of major depressive disorder, may be confused with binge eating episodes in BN (Mury, Verdoux, & Bourgeois, 1995). However, hyperphagia in major depressive disorder indicates an increase in appetite resulting in a general pattern of overeating, whereas binge eating in BN is not fully driven by an increase in appetite (Haedt-Matt & Keel, 2011b), is episodic, alternates with periods of dietary restriction, and is associated with the experience of a loss of control over eating.

Dysthymia occurs in 12.7% of individuals with BN, making it approximately four times more common in BN than in the general population (Hudson

et al., 2007). Dysthymia in adolescence has been shown to be a risk factor for the development of BN in one longitudinal study (Perez, Joiner, & Lewinsohn, 2004); however, it has also been argued that the onset of dysthymia and other depressive disorders is secondary to the effects of the eating disorder (Troop, Serpell, & Treasure, 2001). For example, O'Kearney and colleagues (1998) have suggested that the higher prevalence of dysthymia in bulimic syndromes may be a reflection of the greater distress caused by lack of control over eating as well as the secondary effects of BN. Because dysthymia can be diagnosed only when it is currently present, it is, of course, difficult to evaluate its independence in eating disorder samples.

In addition to major depressive disorder and dysthymia, recent data from the NCS-R indicate that the lifetime occurrence of bipolar disorder is significantly elevated (4.7 times greater) in individuals with BN than in the general population (Hudson et al., 2007). It has been proposed that mood dysregulation observed in BN overlaps with core features of bipolar disorder and may represent a shared diathesis (Fairburn & Harrison, 2003).

Similar to AN and BN, BED is associated with elevated prevalence of lifetime mood disorders. Hudson et al. (2007) reported that individuals with BED were over three times more likely than members of the general population to have a lifetime mood disorder, whereas such a disorder is estimated to be present in up to 46% of BED participants. Among individuals with BED, having a comorbid mood disorder has been associated with significantly elevated levels of eating disorder psychopathology and distress (Peterson, Miller, Crow, Thuras, & Mitchell, 2005). Major depressive disorder is the most common comorbid mood disorder in BED. According to data from the NCS-R, major depressive disorder is over twice as likely to occur in individuals with BED as in the general population, affecting approximately 32.3% of those with BED (Hudson et al., 2007). Like the symptom overlap observed between BN and major depressive disorder, there is evidence that dysphoric mood states associated with major depressive disorder may be secondary to features of the eating disorder. For example, feeling disgusted with oneself over the amount of food being consumed is an associated feature of BED that is a direct consequence of bingeing. In contrast to hyperphagia, which implies that food intake is a result of an increased appetite, binge episodes in BED are not motivated by physical hunger (Haedt-Matt & Keel, 2011b). Rather, increases in negative affect appear to trigger binge eating (Haedt-Matt & Keel, 2011a). Thus, negative affect, which is a core feature of major depressive episodes, may serve as an antecedent to binge eating episodes in BED.

Dysthymia is 3.6 times more common in individuals with BED than in the general population (Hudson et al., 2007). As in the case of the relationship between major depressive disorder and BED, it is unclear whether the persistent, low-grade depressive symptoms and low self-esteem that are key features of dysthymia are a result of the eating disorder or whether binge eating itself is rooted in the pervasive tendency to be emotionally distressed (Stice et al., 2001). It has therefore been proposed that individuals with BED lack adaptive affect-regulation skills, thus increasing the risk for both dysthymia and BED (Telch & Stice, 1998).

In addition to major depressive disorder and dysthymia, there is evidence that the prevalence of bipolar disorder is approximately 3.6 times higher in individuals with BED than in the general population, occurring in approximately 12.5% of individuals with BED (Hudson et al., 2007). Although one of the associated features characteristic of binge eating in BED (i.e., eating more rapidly than usual) may be compared with the increased behavioral activation that is observed in a manic episode, the association between negative affect and binge eating suggests that this feature is unlikely to be linked to behavioral activation. Taken together, findings support that AN, BN, and BED are associated with an increased risk for major depressive disorder and dysthymia, but only BED and BN show higher associations with bipolar disorder than would be expected in the general population.

Anxiety Disorders

Anxiety disorders have been found in 45.8% to 62.9% of patients with AN (Bulik et al., 1997; Fornari et al., 1992; Halmi, Eckert, Marchi, & Sampugnaro, 1991), 31.2% to 64% of patients with BN (Brewerton et al., 1995; Bulik et al., 1996, 1997; Keel et al., 1999), and 29% to 34.7% of patients with BED (Bulik et al., 1997; Halmi et al., 1991). Although one might anticipate inflated comorbidity estimates from patients samples, data from the NCS-R indicate similar or even higher lifetime prevalence estimates for anxiety disorders in AN (47.9%), BN (80.6%), and BED (65.1%). Higher estimates of anxiety disorders from the NCS-R may reflect overlap of symptom features between eating and anxiety disorders that would

result in a second diagnosis from lay interviewers in an epidemiological study. However, much of this appears to reflect true comorbidity between eating and anxiety disorders.

Among anxiety disorders diagnoses, obsessive compulsive disorder (OCD), social phobia, specific phobia, and generalized anxiety disorder (GAD) were the most common in individuals with AN (Godart, Flament, Lecrubier, & Jeammet, 2000; Hudson et al., 2007). Studies have shown that OCD occurs in a substantially higher percentage of women with AN than would be expected in non–eating disordered populations (Steinglass et al., 2011). Godart and colleagues (2003) reported significantly higher lifetime rates of OCD among women with AN (24.3% in ANR and 23.6% in ANBP) compared with 5.4% in matched controls. Prevalence estimates of OCD in AN may be inflated by overlap between features of AN and OCD. For instance, food-related obsessions and compulsions are common in AN, such as cutting food into a certain number of pieces or eating meals at exactly the same time each day (Herpertz-Dahlmann, Wille, Holling, Vloet, & Ravens-Sieberer, 2008). Some of these rituals may be used to support severe dietary restriction by slowing the rate of eating. In addition, results from a study of the consequences of starvation in conscientious objectors (Keys, 1950) indicate that food-related rituals and obsessions may be secondary to malnutrition. Given the potential for symptom overlap, it is necessary for clinicians to assess whether the content of obsessions and compulsions extends beyond concerns with food, eating, and body weight or shape. Evidence supports that both ordering and washing rituals are common in AN patients and that OCD may predate onset of AN (Fornari et al., 1992; Godart, Flament, Perdereau, & Jeammet, 2002), supporting increased risk for OCD in patients with AN. Of note, the NCS-R did not find any cases of OCD in individuals with a lifetime history of AN (Hudson et al., 2007); however, this may reflect the relatively small number of individuals with a lifetime diagnosis of AN in this study ($N = 18$).

In addition to OCD, Godart and colleagues (2003) reported an elevated prevalence of social phobia in women with AN (37.8% in ANR and 41.8% in ANBP) compared with matched controls (5.4% and 12.7%, respectively). The prevalence of social phobia reported in the NCS-R was lower, indicating that 24.8% of people with AN had a comorbid diagnosis of social phobia (Hudson et al., 2007). Fear of eating in front of others represents a source of potential symptom overlap between social phobia and associated features of AN. For a patient with AN, this fear may be attributed to concerns that others will observe her abnormal eating patterns (severe restriction, cutting food into small pieces, combining foods into unusual or unappetizing concoctions). Body image distortion in AN may contribute to fears that others will think the patient is too fat or is eating too much. In such instances, the fear of evaluation from others is directly related to the presence of an eating disorder and a diagnosis of social phobia should not be given. However, social phobia has been diagnosed prior to the onset of AN in almost half of all cases of comorbid social phobia and AN (Godart et al., 2000), and sensitivity to negative evaluations by others may reflect a common cause for both AN and social phobia.

Specific phobias are often comorbid with AN. According to the NCS-R, specific phobias are twice as likely to be present in individuals with AN, occurring in 26.5% of those with a lifetime diagnosis of AN. There appears to be less overlap between features symptomatic of AN and those that are symptomatic of a specific phobia. Some have argued that individuals with AN may be more susceptible to fear conditioning, which could increase the risk for developing an intense fear of becoming fat, specific phobias, and other anxiety disorders (Strober, 2004).

Research has indicated that 48.8% of women with ANR and 45.4% of those with ANBP had a lifetime diagnosis of GAD compared with 3.6% and 10.9% of matched controls, respectively (Godart et al., 2003). Although some studies have reported elevated rates of GAD in AN, estimates from the NCS-R suggest that GAD may not be more common in individuals with AN than it is in the general population (Hudson et al., 2007). Prior to making a concurrent diagnosis of GAD and AN, it would be necessary to ensure that pervasive anxiety and worry were unrelated to food-, shape-, and weight-related concerns and occurred independently of major depressive episodes (Pallister & Waller, 2008).

In BN patients, PTSD, OCD, agoraphobia without panic, social phobia, and specific phobia are among the most common comorbid anxiety disorders. Like patterns of onset in AN, there is evidence that the anxiety disorder preceded the onset of BN in up to 71% of women diagnosed with BN and an anxiety disorder (Brewerton et al., 1995).

This suggests that anxiety disorders may in some way predispose individuals to the development of BN (Bulik et al., 1996).

According to data from the NCS-R, approximately 45% of individuals with BN have a lifetime diagnosis of PTSD (Hudson et al., 2007). While PTSD and BN do not share core criteria, there is evidence that several of the associated features of PTSD and BN overlap (Beales & Dolton, 2000; Mazzeo, Mitchell, & Williams, 2008). Specifically, alexithymia and dissociation have been described in individuals with BN and PTSD. It has also been proposed that bingeing and/or purging may serve as a means of escape from PTSD symptoms (Mitchell, Mazzeo, Schlesinger, Brewerton, & Smith, 2012). Finally, traumatic experiences that form a core criterion for a diagnosis of PTSD may increase the risk for the development of BN and syndromes characterized by binge eating (Keel, Holm-Denoma et al., 2011).

OCD has predominately been associated with features of AN; however, there is evidence that it is related to BN as well (Godart et al., 2003). According to data from the NCS-R, 17.4% of individuals with BN have a lifetime diagnosis of OCD, making them over seven times more likely to be diagnosed with OCD than are members of the general population (Hudson et al., 2007). Some reports of OCD in BN fail to distinguish symptoms of the eating disorder from symptoms of an anxiety disorder. For example, compulsive exercise reported by an individual with BN to ensure that she burns the exact number of calories consumed during a binge episode would be describing an inappropriate compensatory behavior, which is among the criteria for BN. Double counting this behavior as a symptom of both OCD and BN runs the risk of identifying two disorders when one disorder could account for the full clinical presentation. According to Matsunaga and colleagues (1999), however, there is evidence that BN patients with co-occurring OCD frequently display OCD symptoms related to symmetry, contamination, and checking. These findings indicate that obsessions and compulsions in patients with BN are not circumscribed to thoughts and behaviors related to food, shape, and weight, thus supporting a separate OCD diagnoses in these patients.

Agoraphobia without panic is nearly nine times more common in individuals with BN than in the general population, according to the NCS-R (Hudson et al., 2007). However, other studies have reported varying results regarding the lifetime prevalence of agoraphobia in BN, ranging from 0% to 17.4% (Laessle, Wittchen, Fichter, & Pirke, 1989; Schwalberg, Barlow, Alger, & Howard, 1992). Similarly, there are conflicting data regarding the relationship between GAD and BN. Data from the NCS-R did not indicate a higher prevalence of GAD in BN than in the general population; however, Godart and colleagues (2003) reported significantly higher rates of GAD among patients with BN, such that 36.7% of women with BNP and 26.3% of women with BNnP had a comorbid GAD diagnosis, compared with 10.9% of matched controls, potentially reflecting increased comorbidity in a treatment-seeking sample.

Several studies support elevated prevalence of social phobia in BN (Bulik et al., 1997; Garfinkel et al., 1995; Godart et al., 2003). Social phobia was reported in 41.3% of individuals with BN in the NCS-R, reflecting a nearly fivefold increase in risk (Hudson et al., 2007). In examining comorbidity between BN and social phobia, it is important to disentangle this symptom from preoccupations with eating, food, and body weight/shape that are common features of eating disorders. For example, fears of others observing a binge eating episode would not reflect social phobia as much as a normal concern about others observing abnormal behavior. Additionally, once friends and family are aware of an eating disorder, discomfort with eating in the company of the "food police" does not represent a social phobia. Striegel-Moore and colleagues (1993) found that specific symptoms of social anxiety among individuals with BN were significantly associated with body dissatisfaction, suggesting that the prevalence of social phobia in BN may be inflated by overlap between anxiety symptoms and features associated with BN. Garfinkel and colleagues (1995) reported significantly higher lifetime rates of specific phobia in BN (40%) compared to controls (11.4%), and population-based data from the NCS-R indicate that 50% of individuals with BN had a lifetime diagnosis of specific phobia, consistent with estimates reported by Garfinkel et al. (1995) and reflecting a more than fivefold increase in risk. Across anxiety disorders examined in the NCS-R, all but one (GAD) demonstrated an increased prevalence in BN compared with the general population, supporting elevated comorbidity between BN and anxiety disorders.

Compared with AN and BN, less research has been conducted on the comorbidity of anxiety disorders and BED. Based on the NCS-R, approximately 65% of individuals with BED have a comorbid anxiety disorder in their lifetimes and, notably, all

anxiety disorders are significantly more prevalent in individuals with BED compared with the general population (Hudson et al., 2007). Among anxiety disorders in BED, social phobia, PTSD, and specific phobia are estimated to be the most common. Eating alone owing to embarrassment over the quantity of food being consumed and feelings of disgust with oneself after binge eating are features associated with binge eating in BED that may overlap with associated features of social phobia (e.g., fear of eating in front of others) (Sawaoka et al., 2011). However, in social phobia, this concern should extend to all eating episodes, including regular meals and snacks, whereas this concern and embarrassment would be restricted to binge eating episodes in BED. Studies have shown that individuals with BED exhibit increased sensitivity to the evaluations of others (Reas, Grilo, Masheb, & Wilson, 2005). Social phobia in individuals with BED may thus reflect efforts to avoid negative evaluation regarding one's weight, driven by appearance-related concerns. However, a recent study by Sawaoka and colleagues (2011) concluded that the high rate of social anxiety in BED is not attributable to excess weight among individuals with BED, as social anxiety was not significantly associated with body mass index (BMI). PTSD is five times more likely to be reported by an individual with BED and has been reported to fully or partially mediate the relationship between trauma and disordered eating (Brewerton, 2007). In addition, bingeing as a means of escape or dissociation has been implicated as potential overlap in features of BED and PTSD (American Psychiatric Association, 2013). The high rate of comorbidity between BED and specific phobia (37%) is not fully understood (Hudson et al., 2007) but—given the increased risk of specific phobia in AN, BN, and BED—may reflect processes that occur across eating disorder diagnoses.

Substance Use Disorders

Elevated prevalence of both alcohol and nonalcohol psychoactive substance abuse and dependence has been observed in eating disorders (Hudson et al., 2007). Dependence on both illicit drugs (marijuana, crystal meth-amphetamine, cocaine) and prescription medicines (dexedrine, diazepam [Valium]) has been reported as well. Alcohol dependence is more common than dependence on illicit drugs in both AN and BN (Hudson et al., 2007), likely reflecting increased access to alcohol, even for underage drinkers, compared with drugs that are illegal for all age groups.

Unlike mood and anxiety disorders, there does not appear to be as much direct symptom overlap between eating and substance use disorders. However, many drugs influence appetite and may be used to facilitate dietary restriction (e.g., psychostimulants) or may precipitate binge eating episodes (e.g., marijuana). In addition, there may be symptom homology. The overconsumption of psychoactive substances may be driven by the same mechanisms that contribute to overconsumption of food. In both cases, a person may be seeking a high from the rewarding aspects of these behaviors (Wang et al., 2011) or may be seeking escape from negative emotional states through these behaviors (Berking & Wupperman, 2012).

Alcohol use disorders have been reported to be absent or underrepresented in ANR (Eddy et al., 2002; Halmi et al., 1991). In contrast, elevated rates have been reported in ANBP, and significant differences have been reported between the two subtypes on this variable (Eddy et al., 2002; Root et al., 2010a,b). Thus, the range of lifetime prevalence rates for alcohol use disorders (0% to 33%) is quite wide for AN (Eckert, Golber, Halmi, Casper, & Davis, 1982; Henzel, 1984; Halmi et al., 1991; Root et al., 2010a). Because alcohol is caloric, it is not surprising that individuals who severely restrict caloric intake would be at decreased risk for alcohol use disorders compared with the general population. However, most individuals with AN fall within the binge-purge subtype, potentially explaining the elevated odds ratios for alcohol use disorders in AN reported in the NCS-R (Hudson et al., 2007) and in a population-based Swedish twin sample (Root et al., 2010a). Overall, individuals with AN appear to be two to three times more likely to have an alcohol use disorder than members of the general population.

According to the NCS-R, individuals with AN have increased risk for illicit drug use disorders (present in 17.7% with an odds ratio of 3.4) but not specifically for illicit drug dependence (present in 5.2%) (Hudson et al., 2007). Non–alcohol use disorders have been reported in 0% to 10% of patients with AN (Halmi et al., 1991; Laessle, Kittl, Fichter, & Wittchen, 1987; Root et al., 2010b), with reduced prevalence in those with the restricting subtype of AN (Eddy et al., 2002; Root et al., 2010b). Interestingly, the active ingredient in marijuana, tetrahydrocannabinol (THC), was tested as a treatment for food restriction in AN (Steinglass & Walsh, 2004). However, the medication was poorly tolerated because patients did not enjoy the

altered mental state produced by THC (Steinglass & Walsh, 2004).

According to the NCS-R, individuals with BN have a sixfold increase in risk for alcohol dependence, with over a third of individuals meeting criteria for alcohol abuse or dependence (Hudson et al., 2007). Similarly, over 20% of Swedish twins with a lifetime history of BN endorsed a lifetime history of alcohol abuse or dependence, reflecting a more than fourfold increase in risk compared with the general population (Root et al., 2010a). Consistent with these population-based estimates, rates of alcohol use disorders in BN patient samples have ranged from 32.4% to 42% (Braun, Sunday, & Halmi, 1994; Keel et al., 1999).

While alcohol use disorders are more common than illicit substance use disorders in BN (Hudson et al., 2007), non–alcohol substance use disorders have been reported in 21.9% to 32.9% of patients with BN (Bulik et al., 1997; Keel et al., 1999) and 26% of individuals with BN from the community (Hudson et al., 2007). Individuals with BN have an eightfold increase in risk (Hudson et al., 2007). Among illicit substances, marijuana is the most commonly abused (Haedt & Keel, 2005) and may increase the risk for binge eating episodes owing to the appetite-enhancing effects of THC. Individuals with BN have also reported a particular affinity to cocaine and amphetamines (Haedt & Keel, 2005), noting the benefits of elevated mood and energy and decreased appetite as desirable effects of these stimulants.

Approximately 12.4% of individuals with BED meet criteria for alcohol dependence over their lifetimes and another 9% meet criteria for abuse, resulting in elevated odds ratios for both dependence (2.7) and abuse or dependence (2.2) (Hudson et al., 2007). Although results from a population-based Swedish twin registry did not find elevated prevalence of alcohol use disorders in BED (14%) compared with that in the general population (6%), the relatively small sample of twins with BED (n = 49) may have limited power for supporting comorbidity. Particularly interesting is that estimates of disorders involving the illicit use of drugs are comparable to estimates for alcohol use disorders in BED—19.4% of individuals with BED meet criteria for an illicit drug use disorder compared with 21.4% who meet the criteria for an alcohol use disorder (Hudson et al., 2007), suggesting that accessibility is not a primary factor influencing substance use disorder prevalence in BED. Based on data from the NCS-R (Hudson et al., 2007), elevated prevalence of any substance use disorder has been found in AN, BN, and BED (see Table 11.1).

Comorbidity Models and Supporting Evidence

This section reviews theoretical models that may explain comorbidity patterns observed in eating disorders and the evidence in support of each. Figure 11.1 depicts different comorbidity models and is adapted from models presented in Wonderlich and Mitchell (1997).

Common Cause Models

In the basic common cause model, one shared diathesis contributes to the development of eating disorders and comorbid disorders (see Figure 11.1a). If the common cause were familial (residing within either the family environment or genes), one would expect increased rates of the comorbid disorder in the relatives of individuals with an eating disorder (eating disorder proband) because the eating disorder would signify the presence of an underlying cause that contributes to the development of comorbid disorders. For example, if maladaptive affect regulation skills represent a shared familial diathesis between BN and mood disorders, then relatives of BN probands would be at increased risk for both BN and mood disorders. Further, one would expect to find increased rates of mood disorders in relatives of BN probands even when the proband does not have a mood disorder. For most disorders, this is not true (Kaye, Lilenfeld, Plotnicov, 1996; Lilenfeld et al., 1998). Rates of mood and substance use disorders are elevated in relatives of eating disorder probands only when the eating disorder proband also has the comorbid disorder (Kaye et al., 1996; Lilenfeld et al., 1998).

In contrast to these findings, rates of obsessive-compulsive personality disorder are elevated in the relatives of AN probands even when the proband does not herself have obsessive-compulsive personality disorder (Lilenfeld et al., 1998). In addition, there is evidence of shared liability between anxiety and eating disorders from a discordant monozygotic (MZ) twin design (Keel, Klump, Miller, McGue, & Iacono, 2005). Within MZ twin pairs discordant for an eating disorder, only anxiety disorders demonstrated increased prevalence in non-eating-disordered co-twins of eating disordered probands. Importantly, increased risk of anxiety disorders in co-twins was present even when the eating disordered proband did not herself have a comorbid anxiety disorder. In addition, within MZ twin

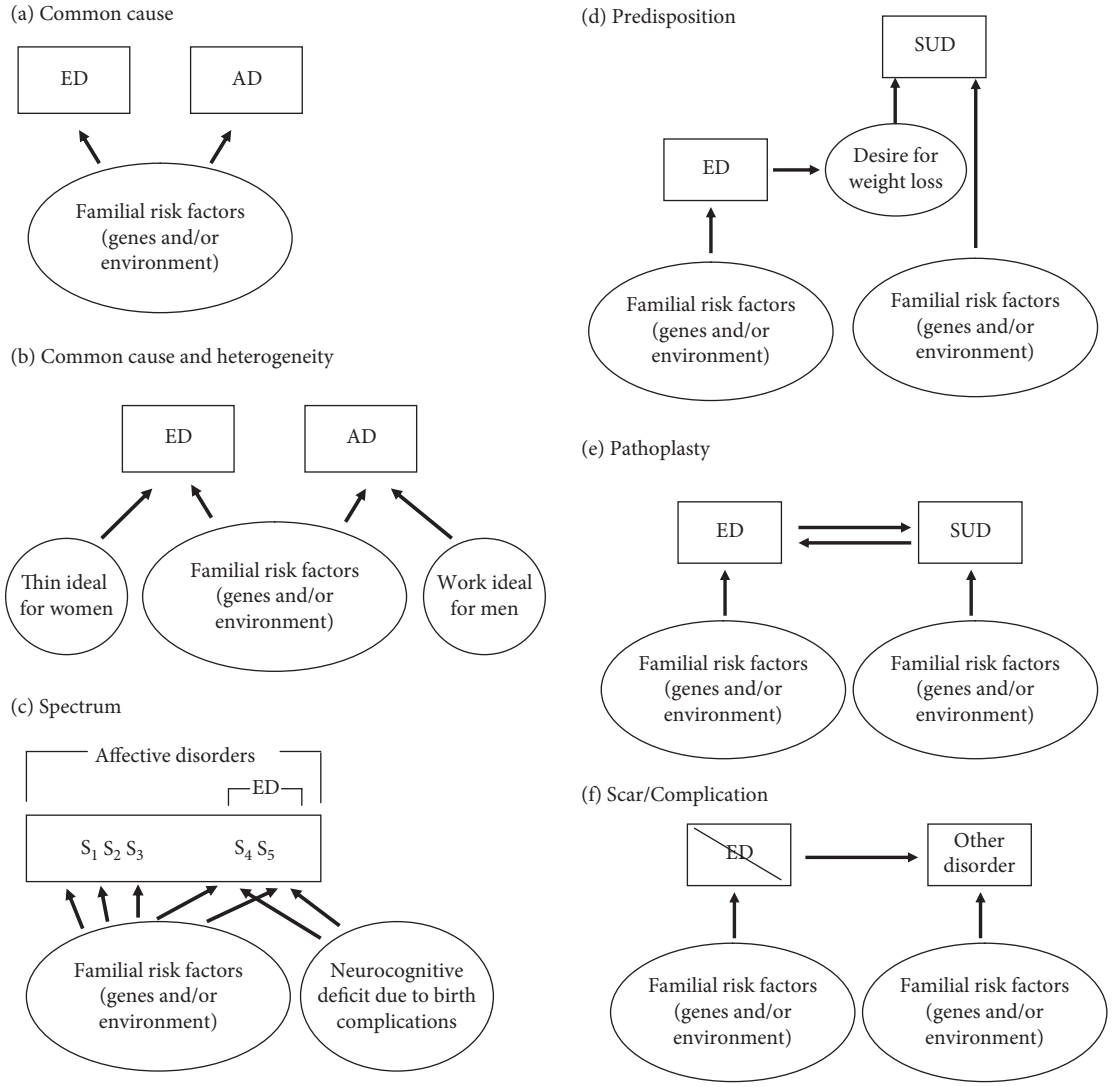

Figure 11.1 Comorbidity models.
a. Common cause
b. Common cause and heterogeneity
c. Spectrum
d. Predisposition
e. Pathoplasty
f. Scar/complication

Adapted with permission from Wonderlich & Mitchell, 1997. Eating disorders and comorbidity: Empirical, conceptual, and clinical implications. *Psychopharmacology Bulletin, 33*(3), 381–390.

pairs discordant for an anxiety disorder, the co-twin unaffected by an anxiety disorder demonstrated an increased risk for eating disorders compared with controls, again even when the anxiety disordered proband did not have a comorbid eating disorder (Keel et al., 2005). Finally, using a twin design, Kendler et al. (1995) found that BN was genetically related to phobias and panic disorder. These studies support shared familial transmission between eating and anxiety disorders; they indicate that elevated comorbidity between eating and anxiety disorders may be explained by a common cause model.

Although eating disorders and anxiety-related disorders appear to share a common diathesis, they do not appear to be equally distributed within the population or within families. For example, anxiety disorders are far more prevalent than eating disorders, and gender differences are greater for eating disorders than they are for anxiety disorders. These patterns suggest that additional, unique factors play into the risk for developing eating disorders—consistent with the common cause and heterogeneity model (Figure 11.1b). In the case of AN and obsessive-compulsive personality disorder,

it is possible that a perfectionistic, rigid personality style represents a common cause for both. However, female gender may contribute to the expression of this liability in the form of an unrelenting pursuit of thinness (characterizing AN), while male gender may contribute to the expression of liability in the form of "excessive devotion to work and productivity" (characterizing obsessive-compulsive personality disorder, APA, 2000, p. 726). In this case, the unique factors (gender roles) are qualitatively distinct from the shared factor (personality).

Like the common cause and heterogeneity models, the spectrum model (Figure 11.1c) explains comorbidity as a result of shared causal factors and imbalance as a result of distinct causal factors. However, both shared and unique causal factors lie on a continuum and are quantitatively related rather than qualitatively distinct. Within the field of eating disorders, James Hudson and Harrison Pope (Hudson, Laffer, & Pope, 1982; Pope & Hudson, 1984) were early proponents of a spectrum model to explain the association between mood disorders and BN and developed the affective variant hypothesis for BN. These authors pointed to the following lines of evidence in support of this model: high levels of comorbidity between BN and mood disorders, high family history of mood disorders in probands with BN (Hudson et al., 1982; Hudson, Pope, Jonas, & Yurgelun-Todd, 1983), abnormal cortisol response to the dexamethasone suppression test in both major depressive disorder and BN (Hudson et al., 1982; Hudson, Pope, Jonas, Laffer, Hudson, & Melby, 1983), and efficacy of antidepressant medications for the treatment of both disorders (Mitchell et al., 1990; Pope, Hudson, Jonas, & Yurgelun-Todd, 1983). In a later paper, Hudson and Pope (1990) posited that affective spectrum disorder included eight disorders (major depressive disorder, attention-deficit/hyperactivity disorder, BN, cataplexy, irritable bowel syndrome, migraine, obsessive-compulsive disorder, and panic disorder) on the basis of these disorders' responsiveness to treatment with three chemically unrelated classes of antidepressant medication. More recently, Hudson et al. (2003) added another six disorders to this list: dysthymic disorder, fibromyalgia, generalized anxiety disorder, posttraumatic stress disorder, premenstrual dysphoric disorder, and social phobia. Broadly speaking, this model is consistent with hierarchical dimensional models in which eating disorders fall within the internalizing spectrum (Forbush et al., 2010).

In a family study to test the presence of a shared familial liability for affective spectrum disorder (ASD), Hudson and colleagues (2003) reported that relatives of probands with at least one form of ASD were 2.5 times more likely to have ASD than relatives of probands without any form of ASD. Interestingly, relatives of probands with ASD were not at increased risk for a substance use disorder compared with relatives of probands without ASD, again supporting distinctions between internalizing and externalizing dimensions of psychopathology (Markon, 2010). However, in examining the risk of specific diagnoses of ASD (e.g., a form of ASD other than major depressive disorder) for relatives of probands with major depressive disorder, only rates of social phobia were found to be significantly higher. Thus the heritability of individual disorders included in the broader category of ASD might contribute to familial transmission of ASD rather than cross-transmission among specific disorders considered to belong to the affective spectrum.

Using a twin design, Kendler et al. (1995) found that BN was not related to the genetic factor that included major depressive disorder. Importantly, much of the supporting evidence for the affective variant hypothesis comes from studies that do not control for the presence of major depressive disorder in BN probands. When individuals have depression in addition to BN, it is reasonable to conclude that the depression contributes to increased rates of major depressive disorder in relatives and may explain abnormal cortisol responses on the dexamethasone test. Indeed, studies that specifically control for depression in the eating disorder proband (Lilenfeld et al., 1998) fail to support the affective variant hypothesis in linking BN to major depressive disorder. Although fluoxetine is FDA approved for the treatment of BN, data regarding the ability of certain medications to effectively treat a range of disorders does not necessarily prove that they share a common cause. For example, aspirin may effectively treat a headache and may reduce risk of a heart attack, but neither headaches nor cardiac arrest are caused by a lack of aspirin.

Notably, family and twin studies are only useful for identifying whether disorders share common genetic or familial causes. Given the significant influence of nonshared environment in risk for eating disorders (Klump, Wonderlich, Lehoux, Lilenfeld, & Bulik, 2002), it is important to consider environmental factors that may not be shared among family members but contribute to development of eating and comorbid disorders. For example, a traumatic event that occurs to one individual within a family may increase risk for both

an eating disorder and a comorbid disorder, such as PTSD. In addition, causal associations may exist between eating and comorbid disorders other than those described within common cause models. For example, unique causal factors may contribute to the presence of an eating disorder, and the presence of an eating disorder or a consequence of the eating disorder, such as malnutrition, may be a causal factor in the development of a comorbid disorder. This causal pathway is reflected by the predisposition model, discussed below.

Predisposition Model

The predisposition model posits that individuals with eating disorders are at increased risk for developing another disorder because the eating disorder forms a diathesis for the other disorder (see Figure 11.1d). In this case, the eating disorder has its own unique causal factors. In addition, the eating disorder precedes the other disorder in time. This model can be distinguished from the common cause models because relatives of eating disordered probands would be at increased risk for a comorbid disorder only if the relative also had an eating disorder. Although the predisposition model also would account for a disorder that precedes an eating disorder in time and increases risk for onset of an eating disorder, the following section and Figure 11.1d focus on the eating disorder as contributing to predisposition for a comorbid disorder.

Findings for alcohol use disorders best fit the predisposition model. Longitudinal research suggests that eating disorders typically emerge before the onset of alcohol use disorders (Baker, Mitchell, Neale, & Kendler, 2010; Herzog et al., 1999), and specific aspects of eating disorders such as overconcern with weight and shape and vomiting frequency predict the onset of an alcohol use disorder (Herzog et al., 1999). Although this could be the result of a third underlying variable that increases risk for both eating and alcohol use disorders—with age-related differences in access to food versus alcohol accounting for the timing of symptom presentation—data from twin and family studies have suggested that BN and alcohol use disorders do not share genetic and familial-environmental influences (Kendler et al., 1995). Family studies have found that neither individuals with alcohol use disorders nor their relatives appear to be at increased risk for eating disorders (Schuckit, Tipp, Anthenelli, & Bucholz, 1996). In addition, relatives of eating disordered probands are at increased risk for a substance use disorder only if they have an eating disorder or if the proband has a substance use disorder (Kaye et al., 1996). Recently, Baker, Mitchell, Neale, and Kendler (2010) described shared transmission between eating disorder symptoms and substance use disorders using a twin design; however, 95% confidence intervals for all associations included 0, suggesting either limited statistical power to detect a significant overlap in genetic and environmental factors or that these syndromes demonstrate independent familial transmission.

In addition to vomiting frequency predicting onset of an alcohol use disorder, longitudinal data suggest that increased vomiting frequency in AN decreased the likelihood of remission from an alcohol use disorder (Franko et al., 2005). In addition, alcohol use disorders increased risk for mortality in AN (Keel et al., 2003) and, when combined with drug use disorders, decreased likelihood of remission from BN at long-term follow-up (Keel et al., 1999). Taken together, these findings suggest that some eating disorder symptoms may predispose individuals to an alcohol use disorder and that eating and alcohol use disorders mutually influence each other's course and outcome. These findings are consistent with the predisposition model, in which aspects of an eating disorder may increase risk for developing a substance use disorder. For example, individuals with eating disorders may be at increased risk for the deleterious effects of alcohol because of their compromised nutritional status. Research in nonhuman primates supports that food restriction increases motivation to work for psychoactive substances, increases total consumption, and decreases extinction of drug-reinforced behaviors (Rodefer & Carroll, 1996, 1999; Rodefer, Mattox, Thompson, & Carroll, 1997). Results from these experimental studies suggest that self-imposed food restriction in eating disorders may increase susceptibility to the development of drug dependence. The influence of the substance use disorders on the course and outcome of the eating disorder is consistent with predictions made by the pathoplasty model.

Pathoplasty Model

In addition to models that posit causal associations between eating and comorbid disorders, alternative models explore phenomenological associations. In these models, each disorder has unique causal factors such that each disorder is established independently (Figure 11.1e). However, the presence of one disorder influences the way in which the other disorder is expressed. The influence of substance use disorders on course and outcome of

eating disorders, despite evidence that substance use disorders neither share familial transmission with eating disorders nor cause eating disorders (as eating disorders typically predate substance use disorders), is consistent with this model. Given that substance use disorders are associated with significant psychosocial impairment and psychosocial impairment predicts eating disorder maintenance and relapse (Keel, Dorer, Franko, Jackson, & Herzog, 2005), substance use disorders may increase chronicity of eating disorders despite not being related to the original causes of eating disorders.

Scar or Complication Model

The scar model is similar to the pathoplasty model in that the presence of an eating disorder influences onlythe expression of the comorbid disorder, not its development. However, the effect is observed after the eating disorder has remitted (see Figure 11.1f). In terms of psychological disorders, few good examples emerge because most psychological disorders are at their worst when the eating disorder is present and tend to abate when the eating disorder remits (Keel et al., 1999). Exceptions to this pattern, such as anxiety disorders, appear to be present prior to the onset of an eating disorder and remain present after disorder remission (Keel et al., 2000). Thus they are unlikely to reflect a scarring effect of the eating disorder. Similarly, it is unlikely that the eating disorder reflects a scar of the anxiety disorder, given evidence of increased prevalence of anxiety disorders in relatives of eating disordered probands even when relatives do not have an eating disorder (Keel et al., 2005).

Clinical Issues Regarding the Comorbidity of Depression and Eating Disorders

Assessment

Although comorbidity between depression and eating disorders remains poorly understood, clinicians are more likely to encounter this combination than any other combination between eating and comorbid syndromes. Comorbid depression may be more readily apparent among patients seeking treatment for an eating disorder, as most are quite candid about their feelings of depression and inadequacy. In addition, self-report measures of depression, such as the Beck Depression Inventory, are widely used in clinical settings. However, comorbid eating disorders may be less evident among patients seeking treatment for depression, given that patients may be reluctant to admit to an eating disorder. Fear of stigmatization of eating disorders, popular misconceptions regarding what constitutes an eating disorder, or fear that treatment will cause weight gain all may reduce the likelihood that patients will volunteer information about their problematic eating. Thus clinicians should routinely inquire about symptoms of depression and eating disorders in patients presenting for treatment of either condition to maximize their ability to develop a treatment plan that will address both. Although the relatively lower prevalence of AN and BN compared to depression may make screening for eating disorders seem unnecessary, eating disorders that do not meet full criteria for AN or BN are highly prevalent among late adolescent and adult women (Field et al., 2012), carry significant risk of death by suicide (Crow et al., 2009), and are more likely to occur among those seeking treatment for depression versus those in the general population owing to comorbidity between depression and eating disorders (Hudson et al., 2007).

Among various screening instruments, the Eating Attitudes Test-26 (EAT-26) is a brief self-report measure with strong psychometric properties, has a clinically validated cutoff score for identifying a likely eating disorder, and is freely available (Garner, Olmsted, Bohr, & Garfinkel, 1982). The EAT-26 has demonstrated measurement invariance in Caucasian and Hispanic women (Belon et al., 2011) and sensitivity in detecting eating pathology in racially and ethnically diverse populations (Austin et al., 2008). This latter features is important because eating disorders occur across ethnically diverse populations (Franko, Becker, Thomas, & Herzog, 2007), with recent studies indicating no significant differences in eating disorder prevalence estimates among African American, Hispanic, Asian, Latino, or Caucasian American populations (Franko et al., 2012; Marques et al., 2011). This, coupled with evidence for equivalent levels of depressive symptoms across ethnic groups (Herman et al., 2011), underscores the importance of screening for eating disorders even when patients do not fit the stereotype of who may suffer from such a disorder.

While there is evidence that eating disturbances and depression occur at similar rates across ethnic groups, epidemiological data indicate that lifetime prevalence of mental health utilization is lower among ethnically diverse groups than for Caucasians with a lifetime history of eating disorders (Marques et al., 2011) or depression (Conner et al., 2010). Caucasian women have significantly higher service utilization rates for eating disorders compared

with Latino, Asian, and African American women (Marques et al., 2011), and African American individuals seek treatment for diagnosable mood disorders at a rate half that of Caucasians (Brown, 2004). One potential reason for the disparity in treatment-seeking behavior may reflect cultural biases within non-Caucasian ethnic groups regarding mental health care and cross-ethnic differences in reporting distress, both of which may render a clinician less likely to inquire about eating pathology or to recognize the need for treatment among ethnic minorities (Franko et al., 2007). Thus the inclusion of a brief eating disorder screen, such as the EAT-26, along with brief screens of depression among standard intake assessments may increase detection of comorbid eating disorders and depression that could otherwise go undiagnosed and untreated.

Treatment

Importantly, both depression and eating disorders can be life-threatening. Thus clinicians must first address any symptoms that impact patient safety or medical stability. For both depression and eating disorders, suicidality needs to be assessed (Joiner et al., 1999) and, when detected, actively treated throughout intervention (Stellrecht, Joiner, & Rudd, 2006). Because physical complications in eating disorders can arise from starvation and severe purging behaviors, patients with eating disorders should be evaluated by physicians to check for medical stability. Severely low weight; rapid weight loss; vital sign abnormalities; evidence of cardiac, kidney, or liver dysfunction; or electrolyte imbalances may require hospitalization to ensure medical stability. Although hospitalization has been found to be highly effective in achieving medical stabilization through weight restoration and cessation of binge/purge behaviors, postdischarge relapse risk is high in the absence of sufficient outpatient treatment.

Given the high prevalence of depression in eating disorder, guidelines developed in the United States (American Psychiatric Association, 2006) and the United Kingdom (NICE, 2004) support the need for clinicians to address depression in patients with eating disorders. Both the APA and NICE Guidelines recommend against use of medication as a sole or primary treatment for AN, given limited evidence for efficacy of any medication in treating AN (Brown & Keel, 2012). The NICE Guidelines further recommend caution in the use of medications for depression in AN as depression may remit following weight gain (p. 64), and the APA Guidelines recommend that decisions regarding the use of medications to treat depression in AN should be deferred until weight has been restored (APA, 2006, p. 20). In addition, both the NICE and APA guidelines suggest that psychotherapy should be the first-choice treatment in patients with comorbid eating and mood disorders.

Various outpatient treatments have demonstrated efficacy for the treatment of depression and for the treatment of eating disorders, including antidepressant medication, family-based therapy, cognitive behavior therapy (CBT), and interpersonal therapy (IPT) (Kaslow, Broth, Smith, & Collins, 2012; Mayer & Walsh, 1998; Murphy, Straebler, Basden, Cooper, & Fairburn, 2012). However, evidence demonstrating that a single treatment will address both depression and eating pathology in a single patient is lacking (Brown & Keel, 2012). For psychosocial treatments, such as CBT, this likely reflects the disorder-focused nature of treatments. For example, CBT for BN begins with the prescription of a regular pattern of eating to interrupt vacillation between severe dietary restriction and binge-eating episodes and has patients complete daily food diaries in which they are asked to record what they have eaten, when and where they have eaten, feelings and thoughts associated with eating episodes, and also any instances of purging as soon as possible in relation to these experiences (Fairburn, 2008). CBT for depression would not include these interventions, and, similarly, CBT for BN does not include behavioral activation. Not surprisingly, although CBT for BN has been identified as a first-line treatment based on its superiority to waitlist control, placebo, and other active treatments (e.g., antidepressant medications, interpersonal therapy) in producing remission from BN, no study has demonstrated that CBT for BN is superior for reducing symptoms of depression compared with alternative treatments among patients with BN (Brown & Keel, 2012).

There has been growing interest in transdiagnostic approaches for treating eating disorders and related problems. Fairburn et al. (2009) compared two forms of enhanced CBT (enhanced to be used for adult outpatients with any eating disorder not characterized by low BMI) with a waitlist control in a randomized controlled trial for eating disorders. The first form of CBT remained focused on eating disorder features, while the second expanded to address problems with mood intolerance, clinical perfectionism, low self-esteem, and interpersonal difficulties, depending upon the patient's clinical

presentation. Of note, 22 patients were excluded from the study for a comorbid Axis I disorder that "precluded eating disorder–focused treatment" (p. 313), reflecting just over 8% of those screened positive for a sufficiently severe eating disorder and age over 18 years. In addition, 76 of the 154 patients randomized were maintained on antidepressant medication at stable levels throughout treatment. Thus the sample included those with comorbid depression but excluded those for whom a treatment focused on eating disorders was deemed unacceptable. Results supported the efficacy of both treatments over waitlist control, with no overall difference between the focused and broad versions of CBT. Attempts to compare the relative efficacy of the broad and focused forms of CBT in "complex" and "less complex" subgroups were hampered by a combination of small subgroup sample sizes and absence of large effect sizes.

Expanding beyond the use of a broad form of CBT to address eating disorders with complex presentations, some have advocated for interventions that would address processes that underlie comorbid depression and eating disorders, such as CBT for clinical perfectionism (Egan, Wade, & Shafran, 2011). Although a handful of studies have provided proof-of-concept evidence that treatment of clinical perfectionism may reduce both eating disorder symptoms and depression (Egan, Wade, & Shafran, 2011), sample sizes and effect sizes have remained too small to support statistically significant differences between treatment and control conditions (Steele & Wade, 2008). The appeal of such an approach is clear if a single intervention could reduce vulnerability to a range of comorbid conditions.

An alternative to developing psychotherapies that address a core vulnerability process is to examine whether medications with demonstrated efficacy for depression and BN separately have efficacy for treating comorbid depression and BN. The U.S. Food and Drug Administration has approved 60 mg of fluoxetine for the treatment of BN (Powers & Bruty, 2009) and 20 mg of fluoxetine for the treatment of depression (Beasley, Nilsson, Koke, & Gonzales, 2000), suggesting that the single medication might be efficacious for both conditions. However, mixed evidence has emerged regarding its success in treating both BN and depressive symptoms simultaneously. Mitchell et al. (2001) found that a 60-mg dose of fluoxetine led to significant reductions in the frequency of binge/purge episodes in patients with BN compared with placebo in a double-blind randomized controlled trial but found no differences between fluoxetine and placebo on levels of depression. In contrast, Walsh, Fairburn, Mickley, Sysko, and Parides (2004) found that 60 mg of fluoxetine was associated with significant reductions in binge/purge frequency and depressive symptoms compared with placebo in patients with BN. Importantly, neither study targeted patients with comorbid BN and depression. Thus differences in the efficacy of fluoxetine for treating depression may reflect differences in baseline levels of depression. Thus far, no studies have examined the efficacy of a single treatment in samples recruited to have comorbid disorders, which would be necessary for ensuring that floor effects did not hamper detection of improvement for either condition. In addition to increasing the likelihood of successful treatment of the eating disorder, early detection of an eating disorder may enhance treatment of depression. For example, understanding that a patient engages in self-induced vomiting in the evenings may contribute to recommendations that medication should be taken in the mornings to make sure that adequate doses are achieved.

In the absence of data supporting the efficacy of a single treatment for comorbid depression and eating disorders, clinicians should determine which disorder is the priority. After safety and medical stability have been addressed, additional factors that may inform treatment priorities are the extent to which disorders interfere with treatment, impact quality of life, and are distressing to the patient. These factors will influence a patient's priorities and motivation to tackle his or her depression and eating disorder. The clinician should also evaluate what evidence-based treatments are available and their relative efficacy. For eating disorders, treatment efficacy varies considerably across diagnoses and developmental stages. Given a choice between a treatment with a large effect size for depression and one with a small effect size for an eating disorder, it would be reasonable to prioritize the disorder that may be more amenable to treatment. Evaluating chronology of onset for the depression and eating disorder and family history of psychiatric illnesses also may help the clinician determine the likelihood that one disorder may improve as a consequence of successful treatment of the other. For example, if depression began around the time of the eating disorder and there is no family history of mood disorders, then a treatment focused on the eating disorder may reduce both the eating disorder and depressive symptoms. Conversely, if depression

predated the onset of the eating disorder and there is a strong family history of mood disorders, it is likely that both the eating disorder and the depression will need to be targeted in treatment and the order will depend upon factors already discussed. Importantly, even when treatment is targeting only one disorder, awareness of comorbid depression and eating disorders may enhance treatment of the disorder of focus.

Conclusion

Eating disorders demonstrate high levels of comorbidity with mood, anxiety, and substance use disorders. Reasonably strong data support shared familial transmission of eating and anxiety disorders, which could account for comorbidity. In contrast, data support that eating disorders may form a predisposition for the development of substance use disorders and that substance use disorders influence the course and outcome of eating disorders. Distinguishing among comorbidity models may have important treatment implications. For example, evidence that substance use disorders influence course and outcome of eating disorders suggests that treatment needs to address both the eating disorder and substance use disorder. Specifically, dietary restriction and vomiting may need to be reduced through behavioral interventions to decrease vulnerability to drug use problems. In addition, reducing substance use may be necessary to increase the likelihood of sustained remission from the eating disorder. Importantly, there are inadequate data to evaluate the validity of most comorbidity models because few studies have large enough sample sizes with appropriate designs to adequately test these models. Even models that can be ruled out on the basis of lack of shared familial transmission (e.g., Kaye et al., 1996; Lilenfeld et al., 1998) or distinct genetic factors (Kendler et al., 1995) have been examined solely from the perspective of genes and shared family environment. Thus they do not exhaust the full gamut of possible etiological factors that could contribute to the co-occurrence of eating disorders and mood, anxiety, and substance use disorders. Identification of shared etiological factors that contribute to comorbidity in eating disorders may contribute to the development of better interventions that target not only eating disorders but also other major sources of psychiatric morbidity. Identification of eating problems through inclusion of reliable and valid screens in standard intake assessments is key to the successful treatment of eating and comorbid disorders.

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CHAPTER

12 Comorbidity of Depression and Conduct Disorder

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Abstract

Both depression and conduct disorders are relatively prevalent and are related to poor long-term outcomes. Despite being characterized by very different symptoms, it is well established that these two disorders co-occur at higher rates than expected by chance, resulting in poorer adjustment for the individual than would result from either problem alone. The term *comorbidity* is usually reserved to refer to the association of diagnosed disorders, whereas *co-occurrence* refers more broadly to the association of levels of symptoms of conduct problems and depression, which are usually calculated with means or possibly symptoms counts. In the past two decades, researchers have focused particularly on the following issues regarding the comorbidity of depression and conduct disorder: (1) possible causal associations of the two problem behaviors (i.e., do depressive disorders tend to onset after conduct disorders or vice versa); (2) theory regarding causes of the association (i.e., common versus unique risk factors for these two problem behaviors); (3) changes across development (i.e., with age); (4) risks from diagnosed disorders versus symptoms that do not reach diagnostic criteria; (5) outcomes or prognosis (e.g., are outcomes more severe for co-occurring problems than for either problem alone, are there distinct patterns of outcomes associated with co-occurring problems). Within each of these areas there is considerable interest in moderation of effects by gender or gender similarities and differences. This chapter reviews findings pertaining to these issues and presents suggestions for future research. In addition, assessment approaches and clinical implications are discussed.

Key Words: conduct disorders, depression, gender, assessment, clinical implications comorbidity, co-occurrence

Introduction

Depression is a widespread disorder; the World Health Organization ranks major depression among the most burdensome of all diseases (World Health Organization, 2002). Likewise, conduct problems are the most common reason for referrals to child mental health clinics in the western hemisphere (Frick, 1998) and have the poorest prognosis for adult adjustment of any childhood disorder (Kohlberg, Ricks, & Snarey, 1984). Thus each area has received a great deal of attention regarding prevention and treatment. It is also well established that these two disorders co-occur at higher rates than expected by chance (Capaldi, 1991; Knox, King, Hanna, Logan, & Ghaziuddin, 2000; Zoccolillo, 1992), resulting in poorer adjustment for the individual than would be result from either problem alone (e.g., Capaldi & Stoolmiller, 1999).

In 1991, in our first study of the co-occurrence of conduct problems and depressive symptoms in sixth-grade boys, we argued that "These two dimensions are characterized by very different symptoms. Symptoms of conduct disorder include physical fighting, using weapons in fights, being cruel to animals, destroying property, and other delinquent acts. Symptoms of depression include loss of energy, loss

of interest and pleasure, apathy, and sleep problems. The archetypical conduct-disordered child would seem very different from the depressed one" (Capaldi, 1991, p. 277). Studies of the factor structures or clusters of mental disorders or their subdromal symptoms almost always find separate internalizing (emotional disturbances such as depression) and externalizing (conduct problems) dimensions (Achenbach & Edelbrock, 1978; Kendler & Gardner, 2011). Yet despite these issues, a low to moderate association is found across these disorders or clusters of symptoms that seems to hold across a wide age range and for both genders. Zoccolillo (1992) reviewed 40 child and 73 adult general population studies of psychiatric disorders and found that, for both sexes, depressive disorders co-occurred with conduct disorder and the antisocial adult disorders far more than expected by chance in childhood, adolescence, and adulthood. As stated by Kovacs, Paulauskas, Gatsonis, and Richards (1988), "How can such qualitatively different disorders develop in the same individuals and exist side by side?" (p. 216). The possible mechanisms behind the associations of depression and other areas of psychopathology considered in this volume—such as anxiety disorders, substance use disorders, and posttraumatic stress disorder—are overall more intuitive than those underlying an association of depression and conduct disorder. It is particularly puzzling that a cluster of individuals with comorbidity of depression and conduct disorder is found in both genders, because males show a higher prevalence of conduct disorders than females and females, starting at puberty, show a higher prevalence of depressive disorders than do males.

The term *comorbidity* is usually reserved to refer to the association of diagnosed disorders (which are coded as present or absent)—in this case the conduct disorders (including conduct disorder and oppositional defiant disorder) and the depressive disorders (including major depressive disorder, dysthymia, and sometimes bipolar disorder). *Co-occurrence* refers more broadly to the association of levels of symptoms of conduct problems and depression, which are usually calculated with means or possibly symptom counts. Whereas clinical diagnoses are helpful for deciding when and how to treat mental disorders, dimensional approaches are critical for understanding developmental processes and the relevant underlying mechanisms as they unfold over time. This is especially important because individuals with subdromal levels of symptoms often show problems similar to those of diagnosed individuals (Klein, Shankman, Lewinsohn, & Seeley, 2009).

Evidence of Comorbidity and Co-occurrence

As discussed by Angold, Costello, and Erkanli (1999), the first quantitative descriptions of comorbidity between classes of child and adolescent psychiatric disorders for the general population were published in 1987; thus, research in this area has been within the past 25 years. In a meta-analysis of studies involving general population estimates of the association between conduct disorders and depression in children and adolescents, Angold et al. (1999) found a median odds ratio of 6.6 for the comorbidity being greater than chance, although odds ratios varied considerably across the studies. Further, Zoccolillo (1992) found that for boys comorbidity of the two types of disorders is most likely to occur in preadolescence and diminish in late adolescence and early adulthood; whereas for girls, comorbidity is most likely from midadolescence into adulthood. Regarding co-occurrence of symptoms (measured continuously), Capaldi (1991) found for the Oregon Youth Study sample of boys at Grade 6 a correlation of $r = .32$ ($p \leq .01$) between the two constructs, and using a cutoff score of .5 standard deviations about the mean, co-occurrence was found for about 45% of the boys who were elevated for either symptom cluster alone. Other studies have consistently found similar low to moderate ranges of correlations between the two problem behaviors across developmental stages (Fergusson, Lynskey, & Horwood, 1996).

Two reviews of the association of these two areas of psychopathology by Angold et al. (1999) and Wolff and Ollendick (2006) shed significant light on potential reasons for the co-occurrence of depression and conduct disorder. Wolff and Ollendick reviewed, in particular, the four main hypotheses that have been proposed for the association of conduct problems and depression; namely that the association may be due to: (1) problems with either referral or informant biases, (2) an artifact of overlapping definitional criteria, (3) one disorder being a causal factor for the other, (4) shared risk factors. Conclusions drawn from these two reviews are that the first two possibilities do not explain the association, because of findings from community-based samples (eliminating referral bias) and with multiple informants (eliminating informant bias), and in the case of (2) largely because eliminating overlapping symptoms does not reduce elevated rates of comorbidity.

In the past two decades, researchers have focused particularly on the following issues regarding the

comorbidity of depression and conduct disorder: (1) possible causal associations of the two problem behaviors (i.e., do depressive disorders tend to onset after conduct disorders or vice versa); (2) theory regarding causes of the association (i.e., common versus unique risk factors for these two problem behaviors); (3) changes in the association across development (i.e., with age); (4) risks from diagnosed disorders versus subclinical levels of symptoms; and (5) outcomes or prognosis (e.g., are outcomes more severe for co-occurring problems than for either problem alone, are there distinct patterns of outcomes associated with co-occurring problems). Within each of these areas there is considerable interest in moderation of effects by gender. In this chapter, we review findings pertaining to these issues and present suggestions for future research directions.

Theories Regarding One Disorder as a Causal Factor for the Other Disorder

DEPRESSIVE SYMPTOMS AS A CAUSE OF CONDUCT PROBLEMS

As discussed by Capaldi (1992), early psychoanalytic theory conceptualized depression as a superego phenomenon, and it was thought that depression could only be manifest in adulthood, when the superego was developed. Observations in the 1960s that children did show some depressive symptoms—but that these were frequently accompanied by other problems, especially "acting out" behaviors—led to the development of the concept of masked depression (Cytryn & McKnew, 1972; Toolan, 1962). The accompanying behaviors were thought to dominate or "mask" those more traditionally associated with mood disturbance. Similarly, low self-esteem, a common characteristic of depression, was thought to motivate delinquent behavior (Gold, Mattlin, & Osgood, 1989). Whereas the concept of masked depression has fallen out of favor compared with diagnosing co-occurring problems without assumptions regarding etiology, there is evidence that at least in some cases conduct problem symptoms follow depressive symptoms. Kovacs et al. (1988) examined the order of emergence of diagnosed conduct disorder and depression and found that conduct disorder postdated depression more often than it predated depression. This trend toward the primary role of depression temporally was contrasted with the fact that the majority of the conduct disorders did not remit with the depression. In addition, the Kovacs et al. sample of 8- to 13-year-olds was selected owing to diagnoses of depression. The peak age for diagnosis of conduct disorder is 15 years. Many of the symptoms are such that they are generally demonstrated only by older children (e.g., "has used a weapon in more than one fight"). If oppositional disorder, which is found in younger children and is related to later conduct disorder, had been diagnosed—rather than conduct disorder—the temporal sequencing may have been different.

In a sample of children aged 7 to 17 years, Carlson and Cantwell (1980) found that children with a diagnosis of depression had only some behavioral problems that were less severe and postdated the onset of depressive symptoms. In children with both conduct disorder and depression diagnoses, however, the behavior problems were more chronic as well as of greater magnitude. As concluded in the review by Wolff and Ollendick (2006), the literature is sparse regarding the possible progression from depression to conduct problems. In fact, the studies they reviewed are primarily the same as the ones reviewed by Capaldi (1992), indicating little further progress in the literature to support the argument that depression leads to conduct disorder.

CONDUCT PROBLEMS AS A CAUSE OF DEPRESSIVE SYMPTOMS

An alternative view, proposed by Gittelman-Klein (1977), is that children in constant conflict with their environment develop secondary depressive symptoms. Patterson and colleagues (Patterson, Reid, & Dishion, 1992) have described the abrasive behavior of children with conduct problems, and conduct problems have been found in numerous studies to lower the quality of the parent-child relationship or lead to parental rejection (Patterson, 1986) and also to rejection by prosocial peers (Dodge, 1983). Patterson and Capaldi (1990) hypothesized that children with higher levels of conduct problems are vulnerable to developing depressed mood because their antisocial behavior interferes with skill development such as academic and social skills, leading to failure experiences at home, school, and with the peer group. Garmezy (1986) posited that failure experiences in childhood may be emotionally similar to the loss events that have been found to trigger depressive episodes in adults and children. The consequences of aggression and failure may become more severe in adolescence, as conduct problems tend to lead to more salient outcomes during this period compared with childhood (e.g., low grades, school suspensions, pregnancy, arrests).

Copeland, Shanahan, Costello, and Angold (2009) examined the association of childhood and adolescent psychiatric disorders and young adult disorders (at age 21 years) for the Great Smoky Mountains Study. They found that adolescent depression significantly predicted young adult depression, but this effect was accounted for by comorbidities, including with adolescent oppositional defiant disorder. In addition, oppositional defiant disorder predicted later depression. Homotypic continuity or significant stability from youth to young adulthood was found for conduct disorder to antisocial personality disorder. Further, as discussed by Wolff and Ollendick (2006), the age of onset for conduct problems appears to precede that for depression (e.g., Zoccolillo & Rogers, 1991). For instance, the National Comorbidity Survey Replication Study found that conduct disorder preceded depression in 72% of cases (Nock, Joiner, Gordon, Lloyd-Richardson, & Prinstein, 2006), and those with either active or remitted conduct disorder had significantly higher risk for developing depression later in life.

Kofler et al. (2011) tested opposing predictions regarding influences from conduct problems to depressive symptoms and symptoms stemming from the failure and acting out theories of association. Using a national sample of adolescents ages 12 to 17 years, they found that growth in delinquency was substantial across these ages for both boys and girls and showed a quadratic pattern peaking at around age 16 years. The level of depressive symptoms was relatively flat for boys across the period but showed substantial and quadratic growth for girls, peaking at about age 17 years. Competing models were tested with cohort sequential latent growth curve modeling. Findings indicated that early (age 12 years) depressive symptoms predicted age-related changes in delinquent behavior significantly better than early delinquency predicted changes in depressive symptoms. Depressive symptoms were a particularly salient risk factor for delinquent behavior in girls. Although the findings appear to provide support for an acting-out theory of depressive symptoms leading to delinquency, the study focused on relatively severe delinquent behavior only and results might have differed if a broader measure of conduct problems had been used.

Lee and Bukowski (2012) used latent growth curve modeling to study the codevelopment of internalizing and externalizing problems in a large sample of Korean fourth graders followed over four years, testing directional effects across domains. Findings indicated that boys and girls followed differing developmental trajectories in both domains in early adolescence. Bidirectional effects were found across domains for boys, whereas only unidirectional effects from externalizing to internalizing problems were found for girls.

In summary, the weight of evidence lends some support to the notion that whereas many youths with conduct problems develop them independently of depression (but later experience some depressive symptoms), some children and youths with depression may also display some conduct problems that may be related temporally to the duration of the depressive symptoms.

Developmental Patterns: Trajectory Studies of Symptom Levels

As discussed by Capaldi, Pears, Kerr, Owen, and Kim (2012), a pattern of early onset and then decreasing overt externalizing behaviors in early childhood has been found in a number of studies (e.g., Gilliom & Shaw, 2004; Mathiesen, Sanson, Stoolmiller, & Karevold, 2009). Both boys and girls show improvement in physical aggression (hitting, biting, and kicking) from ages 2 to 11 years, although girls appear to improve more rapidly than boys from approximately ages 4 to 8 years (Tremblay, Masse, Pagani-Kurtz, & Vitaro, 1996). Thus, for both boys and girls at this age, risk factors may predict to initially higher levels of externalizing (intercept), failure to make normative improvements across childhood (slope), or both.

The few studies that have examined growth in internalizing symptoms in the early years of childhood indicate a contrasting pattern to that for externalizing—namely a gradual increase in internalizing symptoms across early childhood for both boys and girls (e.g., Gilliom & Shaw, 2004; Mathiesen et al., 2009). This may be related to emotional and cognitive developments in the child that enable the parent to recognize and identify the symptoms as internalizing. For both boys and girls, risk factors may predict initially higher levels of internalizing, more rapid growth in symptoms across childhood, or both. In summary, the overall developmental trajectories of externalizing and internalizing symptoms in childhood appear to differ in direction. Consistent with prior work, Capaldi et al. (2012) found that externalizing behaviors in the children of the Oregon Youth Study boys (in adulthood) decreased for both boys and girls across the 6-year period from ages 3 to 9 years, with girls showing greater decreases. Internalizing increased across the

same period, with girls showing greater increases. Correlations between externalizing and internalizing scores within each time point ranged from $r = .33$ to .53, $p < .05$, and did not appear to differ by child gender.

Consistent with the developmental findings of Capaldi et al. (2012), Angold and Costello (2006) note that the approximately 2:1 female:male prevalence ratio for unipolar depression does not appear until adolescence; in childhood, girls do not show a significantly higher rate than boys, and rates are relatively low in both sexes. Angold and Costello argue that this prevalence pattern in adolescence suggests that "some aspect of the maturing female hypothalomo-pituitary-gonadal system may be responsible for inducing and maintaining a substantial proportion of unipolar depressive states" (p. 919).

These findings point to the importance of examining patterns of co-occurrence over time, involving the growth patterns of both conduct problems and depressive symptoms. Much of the early work regarding co-occurrence involved examining associations at one point in time or, at the most, associations across two points in time (e.g., Capaldi, 1992). A relatively recent innovation is to examine heterogeneity in trajectories of conduct problems and depressive symptoms over time and the associations across these (e.g., Wiesner & Kim, 2006). This approach has a number of advantages in that both of these areas of symptoms show developmental changes over time (which differ for boys and girls), and there is significant heterogeneity in patterns among individuals (e.g., high chronic versus moderate or low) that may help to illuminate the nature of their association.

Fanti and Henrich (2010) examined trajectories from ages 2 to 12 years using findings from the NICHD study of early child care involving over 1,200 children. Maternal reports on the Child Behavior Checklist (Achenbach, 1991, 1992) were used to construct trajectories of externalizing and internalizing problems. Latent class growth analysis indicated three trajectories of internalizing problems (low, medium, and high), with the lower two trajectories staying relatively flat across the period and the high class increasing in the early years. The five-trajectory model for externalizing problems indicated two relatively high groups, both showing a trend across the period with one dropping down to low levels, a moderate group, and two lower groups both showing decreases. They also modeled 11 joint groups, with 3.7% of the children exhibiting chronic and high co-occurring symptoms. The differing groups were not differentiated by ethnicity. The groups exhibiting pure chronic externalizing problems and moderate internalizing and chronic externalizing problems were overrepresented by boys.

For late childhood to midadolescence, Chen and Simons-Morton (2009) used growth mixture modeling to examine conduct problems and depressive symptoms across grades 6 through 9 (ages 11–12 to 14–15 years) for a large school-based sample. A small proportion of boys (8.8%) and girls (3.7%) were high in both problem areas over time. Among adolescents with the highest levels of conduct problems, only 6.3% of the boys and 6.0% of the girls also experienced the highest level of depressive symptoms. Of those with the highest level of depressive symptom trajectories, 42.9% of boys and 10.2% of girls reported the highest level of conduct problems over time, indicating a high risk for boys. However, only 3.8% of boys were in the high depressive symptoms trajectory, representing a very small group. Overall, these findings do not indicate high concordance of symptoms for the most problematic trajectories.

Diamantopoulou, Verhulst, and van der Ende (2011) used a dual-trajectory modeling approach to examine co-occurring trajectories of depression and delinquency from ages 11 to 18 years for a community sample of adolescents. Findings from conditional probabilities indicated that adolescents following a low-level trajectory on depressive symptoms were most likely to also follow a low-level trajectory on delinquency and vice versa. Adolescents following the increasing depressive symptom trajectory were likely to follow the high-level delinquency trajectory. Among the high delinquency adolescents, more girls than boys were likely to follow a high-level trajectory on depressive symptoms. Note, however, that most youth in this study were in the low depressive symptoms and low delinquency groups. Continuity in externalizing symptoms was seen in that childhood aggression, and childhood delinquency predicted, respectively, boys' and girls' membership in the increasing-high depressive symptoms and high delinquency trajectory group. In addition, childhood depressive symptoms predicted girls' membership in these groups.

Wiesner and Kim (2006) examined co-occurring trajectories of delinquent behavior and depressive symptoms and their correlates in midadolescence from about ages 15 to 17 years for a U.S. sample. The growth mixture models of both boys and girls

showed relatively flat levels of depressive symptoms across this period (ranging from high to low levels). For delinquency, boys showed three relatively flat lower-level trajectories and a quadratic high-level trajectory that peaked at around age 16 years, whereas girls showed two low-level trajectories and a moderate-level trajectory that were all relatively flat. A modest degree of comorbidity was found for the boys, with just 2.4% estimated to follow a joint trajectory of high-level delinquent behavior and depressive symptoms. Being in the high-level delinquency class predicted membership in the high-level depressive symptoms class better than vice versa. The degree of co-occurrence was higher for girls than for boys, which may partly have related to the fact that, with more trajectories for boys, matches were less likely. About 11% of the girls followed a joint trajectory of high-level delinquent behavior and high-level depressive symptoms.

In summary, close convergence of trajectory patterns across conduct problems and depressive symptoms has not yet been found, but this is not surprising given the low to moderate magnitude of the correlational associations and the differing developmental patterns in the two domains (e.g., a group of high-conduct-problem youth who show a distinct peak in delinquency at mid- to late adolescence versus flatter, more linear patterns for depressive symptoms during adolescence). There is some evidence from these studies for the primacy of conduct problems among youth with co-occurring problems. Although some gender differences were found, findings remain inconclusive. Overall, these two domains of psychopathology show co-occurrence in both boys and girls across levels, and the studies tend to identify a small chronic "co-occurring" class that is of about the same prevalence as of co-occurring diagnoses (less than 10%). It is important to consider that different factors may relate to growth or increases and decreases in symptoms for differing classes (i.e., at different levels of severity), as noted in the work of Stoolmiller, Kim, and Capaldi (2005) on prediction to latent classes of depressive symptoms (conduct problems were not examined) from early adolescence to young adulthood. Identifying different factors for specific developmental aspects (i.e., initial level and changes over time) of co-occurrence trajectories also warrant further research.

Shared Risk Factors

There is considerable evidence that conduct problems and depressive symptoms share common risk factors (Wolff & Ollendick, 2006), possibly including both biological and sociocontextual risk factors. Wolff and Ollendick present a model regarding the co-occurrence of conduct problems and depressive symptoms that takes into consideration both shared or common risk factors (e.g., parental depression, negative emotionality) and unique risk factors (e.g., parental antisocial personality disorder, child undercontrol of emotions and attention to hostile cues for conduct disorder, overcontrol of emotions and negative self-concept for depressive symptoms). Considering the fact that Wolff and Ollendick limited their review of common risk factors to parent psychopathology, emotion regulation, and emerging cognitive biases—and the reviewed studies suffered from other limitations (e.g., limited numbers of longitudinal studies or follow-up periods, limited controls)—the conclusion that these specific risk factors related to both problems may be somewhat premature.

Findings from other studies however, provide evidence that supports the shared risk factors argument. Fergusson et al. (1996) assessed the extent to which comorbidity between conduct and affective disorders at ages 15 to 16 years could be explained by common causal factors in childhood versus reciprocal causation between the conditions. Findings indicated that risk factors for conduct disorders overlapped and were associated with the risk factors for adolescent affective disorders, accounting for two thirds of the shared variance. Affiliation with delinquent peers, parental attachment, and family stress in early adolescence were each associated with both conduct and affective disorders, as was a family history of offending. Most of these associations were of a small magnitude, and the correlation explained by common causes was about .14. After accounting for associated causal factors, reciprocal associations between conduct and affective disorders were not significant. Lee and Bukowski's work (2012) on a large Korean sample of fourth graders followed across four years found that risk factors showed some differentiation of prediction by domain and gender, with parental violence a common cross-domain risk factor for boys and affiliation with delinquent friends a cross-domain factor for girls.

FAMILIAL ASSOCIATIONS AND GENETIC STUDIES

There is considerable evidence of familial associations in depression and conduct problems. In prospective three-generational studies, Pettit,

Olino, Roberts, Seeley, and Lewinsohn (2008) and Weissman et al. (2005) found associations in depression across three generations. Intergenerational associations are also found for conduct problems. Capaldi, Pears, Patterson, and Owen (2003) found that father's conduct problems, assessed in adolescence, were predictive of their offspring's more difficult temperament (anger and activity level) at age two years. Conger, Neppl, Kim, and Scaramella (2003) and Thornberry, Freeman-Gallant, Lizotte, Krohn, and Smith (2003) found similar intergenerational associations in angry and aggressive behavior and in antisocial or conduct problem behaviors across generations, respectively. Generally such associations are of a low to moderate magnitude.

Some recent twin studies have examined the contribution of genetic as well as shared and unshared environmental influences to the co-occurrence of internalizing and externalizing symptoms in adolescents. Cosgrove et al. (2011) examined whether a model positing two latent factors of internalizing and externalizing explained the interrelationships among six psychiatric disorders (MDD, two anxiety disorders, ADD/hyperactivity disorder, ODD, and CD) using adolescent report on the DISC (Diagnostic Interview Schedule for Children) to assess disorder. They found support for the two latent factors. The factors were moderately heritable and influenced by significant common genetic and nonshared environmental factors but not by shared environmental factors. In contrast, Pesenti-Gritti et al. (2008) found that covariation of internalizing and externalizing problem behaviors (as assessed by the parent CBCL [Child Behavior Check List]) was best explained by genetic and common environmental factors, whereas the influence of unique environmental factors was nonsignificant.

In another twin study, Singh and Waldman (2010) found that a portion of the genetic influences underlying externalizing symptoms was accounted for by the genetic influences underlying negative emotionality, thus indicating some shared genetic origins. Molecular genetic studies have not yet shed light on what these shared genetic origins might be, as they tend to focus on separate metabolic pathways (e.g., dopamine for conduct problems and serotonin for depression). In addition, there is some evidence that prenatal factors (other than genetic inheritance) may affect conduct problems and depressive symptoms. Ashford, van Lier, Timmermans, Cuijpers, and Koot (2008) found that children whose mothers had smoked during pregnancy had increased levels of both internalizing and externalizing problems over the period of ages 5 to 18 years. These associations remained significant after taking into account internalizing problems for externalizing problems and vice versa, as well as possible confounding variables (e.g., prenatal and perinatal factors, maternal mental health, socioeconomic status).

There is some evidence of cross effects from parent to child that may be because of child early experience rather than to genetic factors. In a twin study, Kim-Cohen, Moffitt, Taylor, Pawlby, and Caspi (2005) found that maternal depression occurring after, but not before, the twins' birth was associated with child antisocial behavior at age seven years. Parental history of antisocial personality symptoms accounted for approximately one third of the observed association between maternal depression and children's antisocial behavior, but maternal depression continued to significantly predict children's antisocial behavior. The combination of depression and antisocial personality symptoms in the mothers posed the greatest risk for children's antisocial behavior, suggesting the significance of early environmental risk for the development of co-occurrence of depressive symptoms and conduct problems.

temperament/affect

It is possible that the irritability and negative affect associated with depression may contribute to increased conflict with others, oppositionality, and subsequent acting-out behavior, and that negative affect is a common risk factor underlying co-occurrence. Early risk for co-occurring conduct problems and depressive symptoms thus may be related to temperament or the experience and expression of emotion. Martin, Boekamp, McConville, and Wheele (2009) found that children's decreased accuracy in sadness perception was associated with increased externalizing symptoms, and also that higher lability for negative emotions was related to externalizing symptoms. Eisenberg et al. (2009) used borderline clinical levels of symptoms of externalizing and internalizing behaviors to define four groups of children using parent and teacher ratings (low symptoms, high externalizing, high internalizing, or high co-occurring problems) and examined symptoms over a four-year period starting at around age six years. Externalizing problems were associated with low effortful control, high impulsivity, and negative emotionality (especially anger), and patterns of change were associated with these factors. Internalizing problems were associated with

low impulsivity, sadness, and somewhat with high anger. However, it did not appear that general negative affect might be an explanation for co-occurring problems at this age, as sad affect was primarily associated with elevation on internalizing problems and anger with elevation on externalizing problems. Overall, the children with co-occurring problems appeared to be the most problematic group. It is possible that at older ages the differentiation of sad and angry affect becomes more blurred, and both may be associated with irritability and conflict.

FAMILY CONTEXT AND PARENTING RISK FACTORS

In one of the first comprehensive examinations of family risk factors related to co-occurring conduct problems and depressive symptoms, Capaldi (1991) created four groups of sixth-grade boys for the Oregon Youth Study sample using a criterion of .5 SD above the mean: namely co-occurring problems, elevated conduct problems only, elevated depressive symptoms only, and low symptom scores. The group with high levels of both conduct problems and depressive symptoms, or co-occurring problems, showed higher levels of family risk in the areas of parental transitions (divorces, repartnerings) and larger numbers of siblings. Compared with the low-problem boys, the mothers of these boys with co-occurring problems were younger at their first birth, and both parents showed higher levels of substance use, with fathers showing higher levels of antisocial behavior. The parents did not show significantly higher levels of depressive symptoms, although there was a trend in that direction for mothers. Regarding parenting, the parents of these boys showed less consistent discipline and poorer monitoring than did the families of the low-problem boys.

Brensilver, Negriff, Mennen, and Trickett (2011) examined the moderating effects of maltreatment experience and gender on associations between depressive symptoms and externalizing behavior across a one-year period in late childhood/early adolescence and found that girls, particularly maltreated girls who exhibited early externalizing behavior, were at high risk for the development of subsequent depressive symptoms. In their study of conduct problems and depressive symptoms trajectories from ages 11–12 to 14–15 years, Chen and Simons-Morton (2009) found that risk factors showed generally similar patterns of associations with the initial level of conduct problems and depressive symptoms, with parent-child conflict being a substantial risk factor in predicting increasing symptoms in each domain over time.

Copeland et al. (2009) applied latent class analysis to 17 psychosocial childhood risk factors. They found a high-risk class (8.6% of the sample) characterized by family relational dysfunction and parental risk characteristics, which included mental illness and crime. This group had the highest rates of both emotional and disruptive disorders and high rates of depression. In summary, these findings suggest that family risk factors are associated with both problem domains, and that youth with high levels of co-occurring symptoms tend to come from multiproblem backgrounds.

STRESS

That stressful events play a role in the etiology of depression is well established (Hammen, 2005; Monroe & Simons, 1991), but their role in relation to externalizing symptoms is less clear. Timmermans, van Lier, and Koot (2010) examined the role of stressful events in the development of externalizing and internalizing behaviors from ages 3 to 18 years for a general population sample. They found that from the age of three years onward externalizing symptoms predicted experiences of stressful events, and in turn the stressful events predicted later externalizing problems. Stressful events also explained part of the continuity of internalizing problems from the age of 10 years onward but not during childhood. From childhood onward, cross influences from externalizing problems to subsequent internalizing problems were found to be mediated through stressful events. Cross influences from internalizing problems to externalizing problems were found only in adolescence, again via stressful events. From childhood onward to late adolescence, stressful events played a significant role in both the continuity and co-occurrence of externalizing and internalizing problems.

OUTCOMES

It is well established that young adults who were diagnosed as conduct-disordered in childhood are at high risk for antisocial personality disorder in adulthood (Robins & Ratcliff, 1979) and pervasive social difficulties (Zoccolillo, Pickles, Quinton, & Rutter, 1992). Children diagnosed with a depressive disorder are also at risk for later major depression (Kovacs, Feinberg et al., 1984) as well as other problems such as anxiety disorder (Kovacs, Gatsonis, Paulauskas, & Richard, 1989).

There is a growing body of evidence regarding both shorter and longer-term outcomes of co-occurring conduct problems and depressive symptoms. In the Capaldi (1991) study described above, the boys with co-occurring problems showed the same skill deficits and problem areas as the single-problem boys but also showed particularly low levels of academic skills and peer acceptance and high levels of early substance use. Adjustment continued to be poor two years later (ages 13 to 14 years) for the boys with co-occurring problems. In addition, these boys showed high levels of suicidal ideation compared with boys in the other groups. Miller-Johnson, Lochman, Coie, Terry, and Hyman (1998) examined the association of the co-occurrence of conduct problems and depressive symptoms at grade 6 with substance use (alcohol, tobacco and marijuana use) at grades 6 through 10 for African American boys and girls. Adolescents with co-occurring problems showed the highest levels of tobacco use at grade 10, although they did not show higher levels of alcohol or marijuana use than adolescents with the conduct problems only.

There are three main ways that co-occurring conduct problems and depressive symptoms may affect future adjustment: (1) an individual with high levels of symptoms in both areas may experience the adjustment problems specifically associated with each form of psychopathology but with no other added risk from co-occurrence, (2) each area of psychopathology may account for unique variance in the outcome (additive model), and (3) an interaction (multiplicative term) of the two problem areas (interactive model). Capaldi and Stoolmiller (1999) examined numerous outcomes at ages 17 to 19 years for young men who had shown elevated levels of conduct problems and/or depressive symptoms at ages 11 to 12 years. They found that both conduct problems and depressive symptoms showed significant stability to young adulthood. Prediction to outcomes was examined in two-step regression models that controlled for the earlier levels of the outcomes and examined interactions. Overall, predictions showed effects of one risk area (Model 1 above), only one additive effect, and no added risk from interactive effects. Conduct problems were associated with a broad range of adjustment problems including continuing problems in peer associations, substance use, self-esteem, relationships with parents, and new problems in noncompletion of education, unemployment, driver's license suspensions, and causing pregnancies. Depressive symptoms predicted particularly to problems in social relationships. Both conduct problems and depressive symptoms showed unique or additive prediction to being fired from work. Although additive and interactive effects did not seem to account for problem outcomes, co-occurrence resulted in problem outcomes in multiple areas; thus the poorest adjustment overall.

In terms of early adolescent outcomes relating to relationship problems, Fanti and Henrich's (2010) study indicated that children who showed chronic externalizing or co-occurring externalizing and internalizing problems over the 10-year period from ages 2 to12 years were more likely to be rejected by peers, be asocial with peers, associate with deviant peers, and engage in risky behaviors. However, children exhibiting relatively pure internalizing problems over time were at higher risk only for being asocial with peers.

Ezpeleta, Domènech, and Angold (2006) examined comorbidity and functioning for a sample of children and adolescents aged 8 to 17 years of age attending an outpatient clinic. Of this sample, 43% were conduct disorders only, 24% depressive disorders only, and 33% were comorbid. They found that comorbidity increased depressive and emotional symptoms and functional impairment. After controlling for other disorders and the severity of symptoms, the comorbid children were more impaired overall than the conduct disorder group, and also more impaired than the depressive disorder group in school, the home, and in relationships with other people. They have recommended that children with this comorbidity will need a comprehensive plan to ameliorate their disturbed functioning in daily life, and also that children with conduct disorders should serve as a target group for the prevention of depressive disorders.

In their dual-trajectory modeling study of delinquency and depressive symptoms from ages 11 to 18 years, Diamantopoulou et al. (2011) examined adult outcomes six years later and found that both boys and girls following high-level trajectories on both problem behaviors reported poorer adult outcomes compared to adolescents following low-level trajectories, including higher levels of anxious/depressive symptoms and of aggressive and delinquent behaviors.

Hammen, Brennan, and Le Brocque (2011) examined the association of depressive history with early child rearing (by age 20 years). They found for women but not for men that depression by age 15 years was a risk factor for greater interpersonal difficulties at age 15 years and for early child rearing,

accompanied by further depression and parenting dysfunction at age 20 years.

Ingoldsby, Kohl, McMahon, Lengua, and Conduct Problems Prevention Research Group (2006) examined outcomes at grade 7 for youth with co-occurring conduct problems and depressive symptoms in grade 5 and found lower academic adjustment and social competence two years later for both the children with conduct problems and those with with co-occurring problems. These two groups also showed high levels of association with antisocial peers and substance use, with the co-occurring group showing particularly high mean levels. Youth showing depressive symptoms only were more similar to those showing no symptomatology at all than to the co-occurring group C. Few gender differences were noted in associations. Co-occurring symptomatology and conduct problems alone demonstrated more stability and were associated with more severe adjustment problems than depressive symptoms only over time.

In summary, there is accumulating evidence that youth with co-occurring conduct problems and depressive symptoms have long-term and pervasive adjustment difficulties largely because each domain alone has long-term adjustment consequences. Consequently such multiple problems are likely to cascade to further problems as youths transition into adulthood.

Assessment and Intervention Strategies

For the purpose of making a clinical diagnosis, diagnostic interviews provide preliminary diagnoses but are relatively lengthy. The Children's Interview for Psychiatric Syndromes (ChIPS) (Rooney, Weller, Fristad, & Weller, 1999; Weller, Weller, Fristad, Rooney, & Schecter, 2000) is designed for use with children ages 6 to 18 years, is worded to be more appealing and comprehensible for children, has one-to-one correspondence with the item content of the DSM-IV, and has the advantage of being shorter than other diagnostic interviews. For depressive symptoms, rating scales that assess symptoms and severity come in versions for child self-reports and also for observer report. In addition to being useful clinically for assessing severity, these are useful for assessing depressive symptoms dimensionally in a community-based sample and thus for research rather than diagnostic purposes. Similarly, for the purposes of understanding the development, causes, and outcomes of CD and ODD, conduct problems are usually studied as they occur within a particular population of adolescents rather than by using diagnostic criteria. Conduct problem behaviors, which generally involve behaviors toward others, are usually easier to observe than depressive symptoms. As discussed by Eddy (2006), a variety of checklists and rating scales are available for such assessment. The most widely used is the Child Behavior Checklist (CBCL) (Achenbach, 1991) with parent, teacher, and youth self-report versions; it includes queries on aggression, delinquency, and hyperactivity symptoms. Together, these symptoms are thought to form the broader category of externalizing behaviors. Also frequently used is the Elliott Delinquency Scale (Elliott, 1983), which queries on a wide variety of behaviors for which an adolescent could be arrested, including both criminal and status offenses.

Regarding prevention, there are some programs with proven effectiveness that address both conduct problems and depressive symptoms. The PATHS (Promoting Alternative THinking Strategies) curriculum (Greenberg & Kusché, 2006) is a primary prevention program that addresses both conduct problems and depressive symptoms and is designed for delivery by elementary and preschool teachers in their classrooms. This socioemotional learning program has been shown to increase protective factors such as emotional understanding, social cognition and social competence, decrease externalizing problems such as aggression (as rated by both peers and teachers), reduce symptoms of depression and anxiety, and promote a harmonious classroom environment. Thus, there are treatment and prevention programs addressing both the externalizing and internalizing domains that have proven efficacy or effectiveness, and are important tools for tackling the development of these co-occurring problems.

Clinical Guidelines

As discussed by Weisz et al. (2012), although there are a number of evidence-based treatments (EBTs) for depression and conduct disorder in youth, these treatments are not incorporated into most clinical practice, partly because the comorbidity of many clinically referred youths do not fit well with protocols designed for single or homogeneous clusters of disorders, as they may lack flexibility. Chorpita and Weisz (2005) designed a modular approach to children with anxiety, depression or conduct problems (MATCH) in which treatment procedures from EBTs for these three disorders (cognitive behavioral therapy for anxiety and depression and behavioral parent training for conduct problems) are structured as free-standing

modules (e.g., modules for self-calming, modifying negative cognitions, and increasing compliance with parents' instructions). The modules thus form a menu of options for clinicians, and decision flowcharts help guide module selection and sequencing (Weisz & Chorpita, 2011). A randomized control trial of MATCH (Weisz et al., 2012) showed that clinically referred youth aged 7 to 13 years of age, with the sample including both boys and girls from diverse ethnic backgrounds, showed significantly steeper trajectories of improvement than did children in usual care and standard treatment. After treatment, the children in the modular treatment condition also had significantly fewer diagnoses than youths receiving usual care, whereas data for children receiving standard manual treatment did not differ significantly from outcomes of usual care. A second intervention, the Incredible Years program, was designed to treat early-onset conduct problems but has also been shown to reduce internalizing symptoms in 4- to 8-year-old children (rated by the mother) using any of three delivery methods, namely parent, child, or teacher training.

Conclusions and Implications for Future Research

Significant comorbidity of conduct disorders and depression or co-occurrence of conduct problems and depressive symptoms is found for a wide range of ages—from early childhood well into adulthood—and for both boys and girls and men and women. It is interesting that the low to moderate association between the two domains is quite robust across development given that the developmental patterns or "growth shapes" of conduct problems and depressive symptoms across time differ considerably. Both areas of psychopathology individually are highly problematic as far as current functioning, prognosis (i.e., relatively high levels of stability or recurrence over time), and negative impacts or outcomes. Outcomes are particularly problematic for those with conduct problems and with co-occurring problems—even though negative effects of interactions of the two domains have not generally been found and there seem to be relatively few areas of additive effects. Conduct problems alone predict a broad range of adjustment problems, and co-occurrence is likely to mean problematic outcomes in additional areas associated with depressive symptoms, particularly relationship and work problems. Overall, the work on longer-term outcomes of comorbidity or co-occurrence in these areas is relatively limited; considerably more work is needed to understand outcomes for both girls and women and boys and men. Despite this, it can be concluded that co-occurrence, or relatively high levels of problems in both domains, must be considered as showing the need for an indicated prevention program or treatment program if diagnoses are present.

Despite theories and some evidence of problems in one domain leading to problems in the other domain, particularly for conduct problems predicting depressive symptoms, there does not seem to be strong evidence of a greater association or co-occurrence of problems in these domains with development (i.e., as children get older). It might be expected that if one caused the other (or there was a transactional association involving mutual causality) that this association would increase with age. However, this is an issue that should be further examined using longitudinal data. Further, study design issues regarding measurement of conduct problems and depressive symptoms indicate the need for further consideration of a possible causal association across these domains. In particular, when studies examine possible causal associations using diagnosed conduct disorder to assess conduct problems, this diagnosis indicates relatively severe behavior and symptoms that tend to occur in older youth but were usually preceded by a history of conduct problems of a less severe nature.

There is evidence for a role of shared risk factors in the etiology of co-occurring depressive symptoms and conduct problems, notably related to parent psychopathology, family problems and disruptions, family conflict and violence, and vulnerability to negative affect. Given the issues discussed of limited findings regarding causal associations between conduct problems and depressive symptoms, further focus on the role of shared risk factors is warranted. Further, we know little about how brain metabolism relates to co-occurrence. A factor that warrants further consideration regarding a possible role in co-occurrence that has been little examined is stress, which may play a meditational role for other risk factors such as family problems. Further examination of the role of stress, including physiological measurement of stress, is needed.

Despite gender differences in developmental patterns of conduct problems and depressive symptoms, there seem to be more gender similarities than differences in the prevalence of co-occurrence of conduct problems and depressive symptoms and in predictors and outcomes. However, gender issues have not been addressed enough for the role of gender to be clear, particularly for outcomes.

There are a number of domains that have not been adequately researched as risk factors for, or particularly as, potential consequences of co-occurrence. Study of substance use in this regard has often included summary measures; therefore association to specific substances or substance families (e.g., tobacco, alcohol, marijuana, classes of other illicit drugs) and to dimensions such as levels of use and issues such as problems and impairment from use need further examination. A number of domains of health risk, particularly related to impulsive behaviors and lack of concern for self and the future, should be further examined. These include health-risking sexual behavior and other health-risking behaviors such as risky driving. A further domain that requires better understanding is suicide, given that this is a severe consequence and that there is evidence of heightened risk from co-occurring conduct problems and depressive symptoms and that both these areas individually are risk factors for suicide. This is a difficult area of study given the low base rate of suicide but clearly one of importance.

Although effective behavior-based prevention and treatment programs are available for children who exhibit externalizing problems (e.g., Reid, Eddy, Fetrow, & Stoolmiller, 1999) and internalizing problems (e.g., Stice, Shaw, Bohon, Marti, & Rohde, 2009), prevention and intervention programs targeting co-occurring symptoms remain limited. One reason for the dearth of such prevention/intervention work is that developmental models have not been produced to specify relevant mediators, moderators, and pathways to co-occurring symptoms. Given the widespread adjustment difficulties for those with co-occurring problems, further research is needed in this direction. A further issue is that treatment programs tend to be designed for single disorders or homogeneous clusters of disorders (e.g., the conduct disorders). However, a very promising new treatment approach based on flexible modules suitable to addressing depression, conduct disorders, and anxiety, the MATCH approach, shows evidence of effectiveness in an RCT (Weisz et al., 2012). This approach is a major advance in the right direction, and prevention programs that incorporate modules for the prevention of conduct problems and depression would be an important next step.

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CHAPTER

13 Depression and Comorbidity: Personality Disorder

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Abstract

This chapter examines the relation between personality disorder (PD) and depression, disorders that are commonly comorbid in clinical and community populations. This comorbidity presents both clinical and conceptual challenges. In anticipation of the upcoming introduction of the *Diagnostic and Statistical Manual of Mental Disorders* (fifth edition; *DSM-5*), we review research on the associations of depression with both PD and traits in order to help bridge the current and future literatures. Issues distinguishing PD and depression are reviewed, including conceptual concerns, the nature of the associations between depression and PD and traits, and current evidence on associations between depression and PD and chief personality trait dimensions. Data are presented from an ongoing study examining associations between depressive symptoms, maladaptive-range personality, and psychosocial functioning using proposed *DSM-5* criteria for depression and PD trait domains and facets. Depressive disorders exhibit large associations with negative affect and more moderate links with positive affect and conscientiousness/disinhibition, though there appear to be even more differentiated patterns of associations at the facet level. However, our understanding of the processes responsible for the associations of PD and depression is still limited. Despite this lack of clarity, the links between depression and PD and traits have important clinical implications for assessment and treatment of both disorders. Assessment approaches and challenges are discussed, as well as the implications of co-occurring PD and traits for the treatment of depressive disorders. Finally, future research directions are summarized.

Key Words: personality disorder, depression, mood disorders, comorbidity, assessment approaches, treatment

Personality disorder (PD) is among the most common comorbidities in depressive disorders, and the most challenging. Clinically, depressed patients with PD can be difficult to treat due to myriad deficits in self and interpersonal functioning, and they have a poorer prognosis than other depressed patients. Conceptually, it is difficult to disentangle depressive symptoms—especially when chronic—from PD and traits, as well as to understand the development and nature of their association. This chapter reviews conceptual issues in distinguishing PD from depression; summarizes evidence on concurrent associations between depression and both PD and major personality trait dimensions, as well as presents new data; examines the nature of the associations between depression and PD and traits; discusses the assessment of PD; and reviews the implications of co-occurring PD and traits for the treatment of depressive disorders.

The chapter was written during the latter stage of the development of the *Diagnostic and Statistical Manual of Mental Disorders* (fifth edition [*DSM-5*]; American Psychiatric Association, 2012), in which substantial revisions to the PD section were proposed. As discussed below, the proposal emphasized traits, borrowed explicitly from the literature on

the structure of normal and abnormal personality. Although the proposal was ultimately not adopted, it was included in a section of the manual for further consideration and will likely influence future revisions. Therefore, we review research on the associations of depression with both PD and traits in order to help bridge the current and future literatures.

Definition of PD

The Current Polythetic Categorical Approach

Beginning with the revision of the third edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM*; American Psychiatric Association, 1987), PD diagnoses have been defined by one or more personality traits, and all have been diagnosed polythetically, which requires meeting a certain number of criteria out of a larger set (e.g., five of nine). However, this creates several problems that complicate understanding depression–PD comorbidity. First, polythetic diagnosis contributes to the well-documented heterogeneity within each *DSM* PD (e.g., Widiger & Trull, 2007), which complicates understanding of depression–PD comorbidity because PD samples—even those purporting all to be diagnosed with the same PD—may be different from each other due to sample-specific variation in diagnostic heterogeneity, leading to inconsistent findings.

Second, each of the *DSM* PDs is considered a distinct entity, without regard for the overall domain structure, one result of which is high within-PD comorbidity. At the same time that the *DSM* evolved from 1980 to 2000, however, considerable progress was made in understanding personality trait structure, converging on a consensus hierarchical model of five major personality trait dimensions known as the Five-Factor Model (FFM). Mapping the *DSM* PDs onto this structure demonstrated clearly that PD comorbidity was explained largely, if not fully, by a common set of personality traits that characterized the PDs in the fourth edition of the *DSM* (*DSM-IV*; e.g., Miller, Bagby, & Pilkonis, 2005; Miller, Reynolds, & Pilkonis, 2004; Widiger & Simonsen, 2005). However, because the *DSM* PDs are not organized structurally, one cannot parse which trait aspects of the PD diagnoses in a given sample underlie the depression–PD comorbidity.

A third problem is that the *DSM* PDs are defined solely in terms of traits that are "inflexible and maladaptive and cause significant functional impairment or subjective distress" (American Psychiatric Association, 1994, p. 630), but the *DSM* provides no guidance for determining either (a) whether individuals' impairment or distress is caused by their personality traits (e.g., vs. their depression) or (b) the threshold between "normal range" and "inflexible and maladaptive" personality traits. Thus, PD-sample severity may vary based on how research groups determine this threshold, which hinders understanding depression–PD comorbidity because severity and comorbidity are themselves correlated (Clark, Watson, & Reynolds, 1995).

A final problem in *DSM* PD diagnosis that obstructs understanding of depression–PD comorbidity is the poor convergent and discriminant validity between PD assessment instruments (Clark, Livesley, & Morey, 1997). This is not a necessary result of the use of a polythetic system, but it is related in that the *DSM* PD diagnostic system lacks a valid measurement model.

Dimensional Models of Personality and PD

Almost since its inception in the third edition of *DSM*, the categorical approach to PD diagnosis was recognized as problematic. As Frances (1980) stated, "to classify disorders into separate types, one ideally requires that they be distinct and mutually exclusive. . . [but] the various personality disorders are not at all clearly distinct from normal functioning or from each other" (p. 1050). Many investigators have proposed replacing the categorical system with a dimensional approach. At least 18 dimensional models of PD have appeared in the literature, 12 of which were mapped by Widiger and Simonsen (2005) onto "a common hierarchical structure" (p. 110) that, not surprisingly, bore strong resemblance to the FFM. Other proposals include (a) integrating across Axis I and Axis II via shared trait dimensions; (b) using the Shedler–Westen Assessment Procedure (Westen & Shedler, 1999), a measure derived from clinical descriptions of patients' personalities; and (c) dimensionalizing the existing *DSM* PDs.

Proposals to integrate across Axis I and II via shared personality dimensions are important theoretically (e.g., see Clark, 2005; Krueger, 2005) but currently have little practical value for formulating diagnoses because our current state of knowledge is insufficient to develop a fully comprehensive diagnostic system. It also is unlikely that a revised PD diagnostic system would be developed based on single instrument, such as the Shedler–Westen Assessment Procedure. Dimensionalizing the *DSM* PDs has had greater traction in the PD literature (e.g., First, 2011). However, although this would

increase the reliability of PD diagnosis, it does little to reduce heterogeneity, explain comorbidity, address the issue of the threshold with normality, or increase discriminant validity (Clark, 1999). Longitudinal studies also have shown that dimensionalized *DSM* PD diagnoses do not predict functional outcomes as well as "approaches that integrate normal and pathological [personality] traits" (Morey et al., 2011, p. 1; see also Morey et al., 2007).

Thus it is worth exploring the integrated dimensional model of PD suggested by Widiger and Simonsen (2005) and extending it in two ways:

(1) The FFM was developed from normal-range personality variation, so most FFM measures (and others that the model can incorporate, e.g., the Eysenck Personality Questionnaire, Eysenck & Eysenck, 1975) are most discriminating in that range (e.g., Walton, Roberts, Krueger, Blonigen, & Hicks, 2008). However, for maximal utility in diagnosis, PD dimensional measures must be expanded to cover more extreme manifestations of the traits they assess.

(2) There are certain personality-relevant dimensions that seldom appear in normal-range personality models and measures (e.g., Dependency) and/or have a different mode of expression in the normal range. For example, the normal-range scale of Absorption (Tellegen & Atkinson, 1974) correlates strongly with Eccentric Perceptions, a measure of schizotypal cognitions (Clark, Simms, Wu, & Casillas, in press), yet the content of the two measures is largely nonoverlapping, suggesting a change in trait expression with extremity. Thus, PD measures whose content covers the dimensions' extremes will be more useful when examining depression–PD overlap from a dimensional perspective.

Proposed Classification for DSM-5

The proposed changes in the definition and diagnosis of PD in *DSM-5* (American Psychiatric Association, 2012) represent a radical departure. The first two criteria are the common core elements of all forms of PD: (A) impairment in self and interpersonal functioning, which together comprise personality functioning, and (B) the presence of pathological personality traits. This reformulation is important because it provides, for the first time, a means of distinguishing PD from trait extremity per se. That is, because depression also has a basis in personality (e.g., Clark & Watson, 1991), when PD is diagnosed based solely on maladaptive trait manifestation—as was intended but not operationalized in all previous editions of the *DSM*—it is impossible to determine whether depressed individuals' personality traits reflect PD or simply are related to their depression. The implications of this for research on depression–PD comorbidity are discussed below, albeit only briefly, because they concern future research rather than the existing literature.

For the purposes of this chapter, the most important aspect of the *DSM-5* PD proposal is its "hybrid" dimensional-categorical nature. For Criterion B, the *DSM-5* proposal provides a set of five higher order personality trait dimensions (domains), each comprised of lower order specific traits (facets). Not surprisingly, this trait set strongly resembles the common hierarchical structure Widiger and Simonsen (2005) described, focused on the dimensions' maladaptive ends: Negative Affectivity (Neuroticism), Detachment (low Extraversion or Positive Affectivity), Antagonism (low Agreeableness), Disinhibition (vs. Compulsivity—the only explicitly bipolar domain), and Psychoticism (needed for a complete description of the PD-trait space and "replacing" Openness, which has been shown not to be relevant to PD). Six specific PD categories (Borderline, Obsessive-Compulsive, Avoidant, Schizotypal, Antisocial, Narcissistic) are differentiated by the particular trait dimensions that characterize them.

For example, Avoidant PD is characterized by the domains of Detachment (specifically the facets of Withdrawal, Intimacy avoidance, and Anhedonia) and Negative Affectivity (specifically, the facets of Depressivity, which crossloads on the Detachment domain, and Anxiousness). In contrast, Borderline PD (BPD) is also characterized by Negative Affectivity, but a broader set of facets—Emotional lability, Anxiousness, Separation insecurity, Depressivity, and Hostility—and by Disinhibition (Impulsivity and Risk-taking). The traits characterizing each *DSM-5* PD were selected by matching them to the *DSM-IV* PD definitions and criteria. For example, *DSM-IV* Avoidant PD is defined as "a pervasive pattern of social inhibition, feelings of inadequacy, and hypersensitivity to negative evaluation" (American Psychiatric Association, 1994, p. 664). "Social inhibition" clearly maps to Detachment—specifically the facets of Withdrawal and Intimacy avoidance; "feelings of inadequacy" maps to Depressivity, whose definition includes "feelings of inferior self-worth," and Depressivity and Anxiousness capture "hypersensitivity to negative evaluation."

Individuals who meet the general diagnostic criteria for PD—that is, they have impairments in personality functioning and maladaptive traits that are "relatively stable across time and consistent across situations," not in the normal range either developmentally and/or culturally and not explained by the direct effects of a substance or general medical condition—but whose trait profiles do not match those of any of the six PD types specified in *DSM-5* meet the criteria for PD-Trait Specified, which also provides for the diagnosis of those *DSM-IV* PDs that are not specifically included in *DSM-5*. For example, the definition and criteria of *DSM-IV* Paranoid PD map closely onto the *DSM-5* trait facet of Suspiciousness, and those of *DSM-IV* Dependent PD map onto the facets of Separation insecurity and Submissiveness.

Implications of PD definitions for comorbidity

The definition and, generally speaking, diagnosis of PD is based on trait inflexibility and maladaptivity, with the assumption that these are inherent in trait extremity. Thus, extant studies of depression–PD comorbidity may be described more accurately as examining depression–personality trait relations, albeit indirectly through the trait configurations of the *DSM* PDs and with difficulty due to high within-PD comorbidity. It may be even more accurate to say that such studies simply have examined personality trait configurations common in individuals with depression because, as mentioned earlier, the *DSM-IV* provided no guidance for diagnosing PD other than via criteria that were intended to be manifestations of each PDs' defining traits. Thus, conceptualizing the *DSM-IV* PDs in terms of their underlying trait configurations may lead us to a better understanding of the extant depression–PD comorbidity literature.

In the future, by examining the trait profiles of depressed individuals with and without PD, we will be better able to determine the extent to which depressed individuals' maladaptive personality traits are inherent in their depression versus reflections of PD comorbidity. Possible outcomes include (a) similar trait profiles in both configuration and elevation, indicating that PD per se has little effect on personality–depression relations; (b) similar trait configurations but differences in elevation, consistent with the established comorbidity–severity correlation; and (c) different trait configurations, suggesting "true" comorbidity (i.e., co-occurrence of distinct disorders), indicating that PD may affect how personality is manifested in depressed individuals.

Prevalence and Impact

PD Diagnoses

As noted above, PD is often comorbid with a wide range of Axis I disorders (Clark, 2007). High rates of comorbidity have been observed in both community and clinical samples, although estimates have varied widely, with rates ranging from 20% to 85% (Corruble, Ginestet, & Guelfi, 1996; Klein, Durbin, & Shankman, 2009). Many but not all studies find that mood disorders are most often comorbid with borderline, avoidant, and dependent PD (Skodol, Shea, Yen, White, & Gunderson, 2010). The variation in findings probably reflects the problems with the current classification system discussed above.

In three recent epidemiological surveys, the 12-month rates of comorbidity between mood disorders and a wide range of PD were assessed in large representative community samples. In the National Comorbidity Survey Replication, Lenzenweger, Lane, Loranger, and Kessler (2007) reported data on 5,692 participants. They found that the prevalence of PD among those with any mood disorder was 38.1%. In an international study of 21,162 participants across 13 countries, Huang and colleagues (2009) reported that 23.6% of respondents with mood disorders met criteria for at least one PD. In the largest study to date, Grant and colleagues (2005) interviewed 43,093 individuals to assess prevalence of personality and Axis I disorders in the National Epidemiologic Survey on Alcohol and Related Conditions. They found that 45.9% with major depressive disorder (MDD) and 54.8% with dysthymic disorder (DYS) met criteria for at least one PD. Schizotypal, borderline, and narcissistic PDs were not assessed, so these rates may be underestimates. These results are consistent with previous research suggesting that dysthymia is associated with a higher rate of PD than MDD (Pepper et al., 1995).

Personality Traits

Given the high rates of comorbidity between depressive and PDs, it is not surprising that depression also exhibits substantial covariation with several personality trait dimensions, highlighting the close interrelations between psychopathology and personality. In particular, MDD and DYS are both associated with high levels of Negative Affectivity (NA) and low levels of Positive Affectivity (PA;

see Kotov, Gamez, Schmidt, & Watson's [2010] meta-analysis). Due, at least in part, to the widely acknowledged limitations of the *DSM-IV* PD categorical diagnostic system (e.g., Clark, 2007), however, comprehending the underlying associations between maladaptive personality traits and depressive symptoms has been difficult.

In this section, we add to the literature summarizing data from an ongoing study by two of us (LAC and ER) examining associations between depressive symptoms, maladaptive-range personality, and psychosocial functioning using proposed *DSM-5* criteria for MDD episodes (MDEs), DYS, and PD trait domains and facets. We collected self-report and interview data from 402 participants (*N*= 150 community and *N*=252 psychiatric outpatients). Of these, 202 patients also completed the Personality Inventory for *DSM-5* (PID-5; Krueger, Derringer, Markon, Watson, & Skodol, 2011), a 220-item measure developed specifically to reflect the proposed *DSM-5* trait system. The PID-5 assesses five higher order trait domains—NA, Detachment, Antagonism, Disinhibition–Compulsivity, and Psychoticism—with multiple facets comprising each domain[1]. We used the Basic Interview for Common Disorders in *DSM-5* (Ro & Clark, 2012b), a semi-structured interview developed for the project to assess the proposed criteria for common mental disorders in *DSM-5*. This interview was modeled after the Mini International Neuropsychiatric Interview (Sheehan et al., 1998).

The subsample mean age was 43.5 (standard deviation = 11.8; range, 19 ~ 68); 63% were Caucasian and 27% African American; 58% were women. Table 13.1 shows correlations of MDE and DYS criterion counts with PID-5 domain and facet scores. Consistent with the literature, MDE and DYS symptoms were positively associated with all PID-5 domains but most strongly with the NA (*r*s = .62 and .57), Detachment (*r*s = .50 and .46), and Psychoticism (*r*s = .43 and .40) domains, respectively. At the facet level, for MDE symptoms, strong associations (≥ .50) emerged for Depressivity, Anhedonia, Emotional Lability, Anxiousness, Distractibility, and Suspiciousness and moderately strong associations (≥ .40) with Withdrawal, Perseveration, Irresponsibility, Impulsivity, and Eccentricity. Correlations with DYS symptoms showed the same pattern at slightly (but not significantly) lower levels.

Overall, facet- and domain-level associations were consistent, with most of the strong facet correlations coming from the NA and Detachment

Table 13.1 Correlations Between *DSM-5* Personality Traits and Depressive/Dysthymic Symptoms

Trait Domains / Facets	MDD	DYS
Negative Affectivity	**.62***	**.57**[†]
Depressivity[a]	**.57***	**.53**
Emotional Lability	**.52***	**.53***
Anxiousness	**.56***	**.51**
Suspiciousness[a]	**.51**	.46
Perseveration	.44*	*.38*
Hostility[b]	*.39**	*.35*
Separation Insecurity	*.37**	*.33*
Submissiveness	.18	.20
Detachment	**.50**	.46
Anhedonia	**.55***	.48
Withdrawal	.44	.44
Intimacy Avoidance	.27	.26
Restricted Affect[c]	.19	.13
Antagonism	.24*	.15
Callousness	.28*	.20
Deceitfulness	.24*	.15
Grandiosity	.14	.06
Attention-Seeking	.10	.06
Disinhibition	*.34*	.26
Distractibility	**.54***	.43
Irresponsibility	.44*	*.37*
Impulsivity	.43	*.37*
Rigid Perfectionism (lack of)	.27*	.28*
Risk-Taking	.09	.06
Psychoticism	.43	.40
Eccentricity	.43*	*.38*
Cognitive Perceptual Distortion	*.39**	*.35*
Unusual Beliefs and Experiences	*.31*	*.33*

Note. Overall *N* = 201 ~ 202. Correlations |.50| ~ |.69| **bolded**; |.40| ~ |.49| underlined; |.30| ~ |.39| *italicized*.

* Highest correlation in row (highest *r*s with .01 of each other are both labeled *).

[a] Also listed under Detachment.

[b] Also listed under Antagonism.

[c] Also listed under Negative Affectivity.

domains. However, a few specific divergent correlations emerged; in particular, although relations with the overall Disinhibition domain were modest (*r*s < .35), Distractibility, Irresponsibility, and Impulsivity—all facets of Disinhibition—had moderate to strong correlations with MDE and DYS symptoms (median *r* = .43, range .37–.54). These findings were consistent with Kotov et al.'s (2010) meta-analysis, in which both Disinhibition and low Conscientiousness related significantly—though generally less strongly than NA and Detachment (low PA)—to MDD and DYS. If replicable, these more specific associations may help to shed light on how these personality domains are related to depression, given that they also, and more typically, are associated with externalizing disorders, such as substance abuse.

One possibility is that NA and Detachment are vulnerabilities that precede depression, whereas Disinhibition/low Conscientiousness are "complications"—temporary changes in personality due to depression (as discussed below). For example, the PID-5 Irresponsibility scale includes items relating to forgetting to pay one's bills or skipping appointments or meetings if one is not in the mood. These behaviors may have a different meaning in the context of depression versus an externalizing disorder. Similarly, PID-5 Distractibility includes several items relating to poor concentration and difficulty in goal pursuit. These also may have a different significance in the context of depression versus a more externalizing disorder such as attention deficit disorder.

More immediately, the proposed reformulation of PD in *DSM-5* (American Psychiatric Association, 2012) makes it much more straightforward than with the *DSM-IV* categorical PDs to predict how these dimensional personality data will affect PD comorbidity. For example, the average correlations of the proposed facets comprising Avoidant PD with MDE and DYS symptoms, respectively, are .40 and .51, whereas those of the proposed facets comprising Narcissistic PD are .06 and .09. Thus the likelihood that depression will be comorbid with Avoidant PD is considerably higher than with Narcissistic PD. These data also make sense from the perspective of the primary personality trait correlates of depression—high NA and low PA (Detachment)—which are the same two domains that comprise Avoidant PD. On this basis, BPD (*r*s = .37 and .38, respectively), Schizotypal PD (*r*s = .33 and .35, respectively), and Obsessive-Compulsive PD (*r*s = .33 and .35, respectively) also have a somewhat increased likelihood of comorbidity with depression, whereas Antisocial PD has a somewhat lower likelihood of comorbidity with depression (*r*s = .22 and .25, respectively).

PD Comorbidity and Impairment

Coexisting personality pathology and MDE and/or DYS symptoms are associated with greater impairment in functioning, both concurrently and over time. For example, in a sample of 210 patients with internalizing disorders (e.g., DYS, generalized anxiety disorder, and panic disorder), Seivewright, Tyrer, and Johnson (2004) found that personality problems at baseline significantly predicted functional impairment at 12-year follow-up, as measured by the Social Functioning Questionnaire (Tyrer et al., 2005), an eight-item self-report measure that combines various aspects of functioning (e.g., relationship, work, finances) to generate an overall functional impairment score. Other studies have examined specific functioning domains in depressed patients with or without comorbid PD. For example, in the Collaborative Longitudinal Personality Disorder Study (Gunderson et al., 2000), patients with DYS symptoms and with (vs. without) personality pathology showed greater impairment in life satisfaction, leisure, and relationship domains but not in work functioning (Hellerstein et al., 2010) assessed by the Longitudinal Interval Follow-up Evaluation (Keller et al., 1987). These differential relations indicate the value of comprehensive and multidimensional functional impairment assessment to explore whether personality pathology is linked to additional—or different types of—impairment in patients with MDD and DYS.

Our factor analyses of a comprehensive set of psychosocial functioning measures yielded two factors reflecting adaptive functioning (Clark & Ro, 2011; Ro & Clark, 2012a). Specifically, one factor reflects basic daily functioning (e.g., starting and maintaining a conversation, starting and maintaining a friendship, taking care of oneself alone for a few days) and the other positive functioning and life satisfaction (e.g., having a sense of autonomy, feeling like life has meaning, being satisfied with one's life). Using this framework, we examined how MDE and DYS symptoms, personality pathology, and their interaction predicted these different types of functioning. We assessed personality pathology using the full criterion score on the Iowa Personality Disorder Screen interview (IPDS), which has a sensitivity of 95.8% and specificity of 64.2% for any PD

using a cutoff of two criteria (Langbehn et al., 1999); this cutoff also best differentiated our community and patient subsamples. For these analyses, we used the full sample mentioned previously (N = 402, although due to missing data, Ns for these analyses ranged from 393 to 397). Mean age was 42.4 (range 18–69); the sample was 57.4% White, non-Hispanic, 32.3% Black, and 64.7% women.

We selected the Satisfaction with Life Scale (Diener, Emmons, Larsen, & Griffin, 1985) to represent the positive functioning factor, and the World Health Organization Disability Assessment Schedule–II (WHODAS-II; World Health Organization, 2000) to represent basic functioning, because specific scales have more clinical utility than factor scores and they produced the same patterns of results as their respective factors.

The IPDS correlated .64 and .67 with the MDE and DYS symptom counts, respectively, indicating the presence of a large, general psychopathology factor. Both the IPDS and depressive symptoms (both MDE and DYS symptom counts) were significant in predicting both positive and basic functioning. Thus the results support the existing literature in that depressive symptoms and personality pathology both were associated with poorer functioning. In addition, there was a significant interaction between depressive symptoms and personality pathology in predicting positive functioning/life satisfaction but not basic daily functioning. Figure 13.1 shows the results for MDE symptoms using the Satisfaction with Life Scale (reverse-keyed to reflect poorer functioning) and the WHODAS-II, using the Aiken and West (1991) method of plotting the estimated functioning scores when the symptom and PD scores are plus or minus one standard deviation of the mean. Specifically, the two types of psychopathology had a simple additive relation to basic daily functioning; however, among patients with high levels of depression symptoms, personality pathology did not contribute additional variance in positive functioning/life satisfaction. Much like the well-established relatively specific relation of low PA to depression, this finding suggests that positive functioning/life satisfaction and depression are closely intertwined, so that personality pathology can affect life satisfaction when depressive symptoms are low but when depressive symptoms are high, life satisfaction is virtually inevitably low, leaving no room for personality pathology to have a further effect.

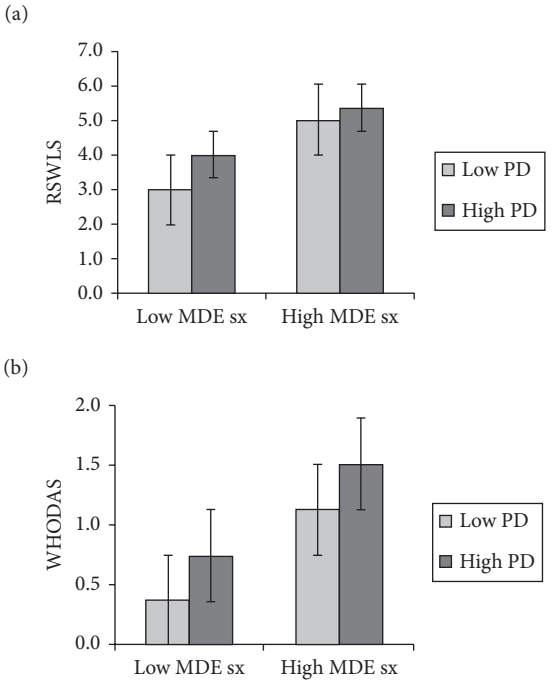

Figure 13.1 Functional differences associated with depressive symptoms and personality pathology.
Note. N = 393–397; MDE = Major Depressive Episode; DYS = Dysthymia; sx = symptoms; PD = personality disorder; RSWLS = (Reversed) Satisfaction with Life Scale; WHODAS = World Health Organization Disability Assessment Schedule, 2nd Edition. Plotted values are estimated functioning scores when the symptom and PD scores are at ± 1 *SD* (Aiken & West, 1991).

Nature of the Association of Depression with PD Traits and Diagnoses

Depression and maladaptive personality traits are interrelated, with some associations stronger and more consistent than others, but the processes through which these associations emerge is less clear. A number of possible explanations have been proposed (Clark, Watson, & Mineka, 1994; Klein, Kotov, & Bufferd, 2011), including (a) there is overlap between the content or diagnostic criteria for depression and personality traits/disorder, (b) both sets of constructs have common causes, (c) personality traits/disorder are precursors of depressive disorders, (d) some personality traits/disorder predispose to developing depressive disorders, (e) personality has pathoplastic effects on the expression or course of depression, (f) personality traits/disorder are state-dependent concomitants of psychiatric symptoms, and (g) personality traits/disorder are consequences (or scars) of psychopathology.

The first explanation views the association between depression and personality traits/disorder as due to overlapping constructs and/or content.

For example, NA is defined by stress reactivity and dysphoric moods, including sadness/depression. BPD currently includes criteria for affective instability, including intense episodes of dysphoria and suicidal behavior.

The common cause and precursor models both view depression and personality as having similar causal influences that account for their association. The *common cause model* views depression and personality traits/disorder as separate constructs that arise from the same, or at least an overlapping, set of etiological processes. The *precursor model* views some personality traits as an early manifestation or "formes frustes" of depressive disorders. Like the common cause account, the precursor model posits that personality and depression are caused by similar etiologic factors. Also, it implies that the relevant traits may have some clinical resemblance to depressive symptoms (suggesting construct/content overlap). However, the precursor model views the association as the product of a developmental process, with the personality trait being evident prior to, and subsequently escalating into, depression. This developmental sequencing distinguishes the precursor model from the common cause account, which views the association between depression and personality as fixed and static.

The predisposition and pathoplasty models differ from the other accounts in that they view personality as having causal effects on the onset or maintenance of depression. Thus, the *predisposition model* holds that personality plays a causal role in the onset of depressive disorders. It is similar to the precursor model in that both propose that the relevant traits are evident prior to the onset of disorder. However, these two accounts differ in that the precursor model assumes that personality and depression derive from the same set of etiological processes, whereas the predisposition model posits that the processes that underlie personality differ from those that lead to depression. As a result, the predisposition account implies a complex interplay among risk factors involving other moderating or mediating variables. The most common example—the diathesis-stress model—conceptualizes personality as the diathesis and stress as a moderator that precipitates the onset of depression. Alternatively, stress may be a mediator, so that personality vulnerability leads to negative experiences (e.g., interpersonal rejection, job loss), which in turn increase the probability of developing depression. In practice, the common cause, precursor, and predisposition models have been very difficult to distinguish (see Klein et al., 2011 for a more detailed discussion).

The *pathoplasty model* is similar to the predisposition model in that it also views personality as having a causal influence on depression. However, rather than contributing to onset, this account posits that personality influences the expression of the disorder after onset. This influence can include the severity or pattern of symptomatology, course, and response to treatment.

The concomitants and consequences models reverse the direction of causality, viewing depression as having a causal influence on personality traits/disorder. In the *concomitants (or state-dependent) model*, assessments of personality are colored, or distorted, by depressive symptoms. This model implies that personality returns to its baseline form after recovery from the depressive episode. In contrast, the *consequences (or scar) model* holds that depressive disorders have an enduring effect on personality, such that changes in personality persist after recovery.

Finally, it should be noted that, rather than being entirely stable, personality traits, and even PD, develop and change over time (Clark, 2007; Durbin & Klein, 2006; Roberts, Walton, & Viechtbauer, 2006). Thus, one can posit dynamic and transactional variants of some of these models (e.g., Klein et al., 2011; Ormel, Oldehinkel, & Brilman, 2001). For example, trait vulnerabilities to depression may change over time, perhaps in response to life events (Middeldorp, Cath, Beem, Willemsen, & Boomsma, 2008). Moreover, these traits may generate stress and alter environmental contexts (Roberts, Kuncel, Shiner, Caspi, & Goldberg, 2007) that subsequently increase or decrease trait vulnerability (Klein et al., 2011).

Studies of the Nature of the Association Between Depression and Personality Traits/Disorder

As there is a larger literature testing models of the association between depression and personality traits than PD, and the proposed *DSM-5* PD diagnostic system explicitly uses traits as PD criteria, we consider traits first.

Traits. A variety of methods and designs have been used to understand the nature of relations between personality traits and depressive disorders. These include examining personality in individuals during and after remission from a depressive episode, comparing personality before and after the occurrence of a first lifetime depressive episode,

examining relations between personality and depression in monozygotic and same-sex dizygotic twins, assessing personality in cohorts of never-depressed individuals and following them to determine whether traits predict who develops depression, and assessing personality in depressed individuals and following them to examine the course of depression. In this section, we focus on high NA (or neuroticism), and low PA (or low extraversion/detachment). Unfortunately, few of these designs have been applied to the facets of NA and PA or to other traits such as conscientiousness/disinhibition.

The issue of construct/content overlap is especially relevant for NA, as dysphoric mood is a key component of both NA and depression, and most measures of NA contain items that are similar to depressive symptoms (Ormel, Rosmalen, & Farmer, 2004). One approach to addressing construct/content overlap is to delete overlapping items and determine whether the association persists (e.g., Lemery, Essex, & Smider, 2002). However, eliminating items risks distorting the nature of both constructs. A better approach is to use designs that assess personality before the onset of depressive episodes or after remission, as discussed below. If personality traits discriminate nondepressed individuals who will develop, or who have recovered from, depression from other nondepressed individuals, it argues against a content overlap explanation and indicates that traits can be distinguished from depressive disorders. As subthreshold levels of depression often precede and follow depressive episodes, this approach would be further strengthened if depressive symptoms are included as covariates in the analyses.

As we discuss below, a number of studies have reported that traits distinguish individuals who will develop or are remitted from depressive episodes, although few of these studies controlled for depressive symptoms at the time of the personality assessment.

One of the best approaches to testing the concomitants/mood state model is by assessing personality when individuals are experiencing an MDE and again after they have recovered. Studies have found consistently that individuals with MDD report higher levels of NA when they are depressed than when they are not depressed (Hirschfeld et al., 1983; Kendler, Neale, Kessler, Heath, & Eaves, 1993; Ormel, Oldehinklel, & Vollebergh, 2004), suggesting that mood state influences reports of NA. The evidence for mood-state effects on PA is weaker and less consistent (De Fruyt, Van Leeuwen, Bagby, Rolland, & Rouillon, 2006; Kendler et al., 1993; Morey et al., 2010).

The influence of mood state on personality should not be overstated, however. Even though levels of NA decline significantly after remission from a depressive episode, individuals' relative positions with respect to levels of NA tend to be moderately well preserved (De Fruyt et al., 2006; Morey et al., 2010). Moreover, Clark, Vittengl, Kraft, and Jarrett (2003) decomposed NA and PA into state and trait components and found that, for each trait, both components were associated with depressive symptoms. Finally, clinical trials indicate that changes in depressive symptoms are not necessarily accompanied by changes in personality (Quilty, Meusel, & Bagby, 2008; Tang et al., 2009).

A related design has been used to test the consequences (or scar) hypothesis. This involves comparing personality measures in depressed individuals before and after an MDE. The results of these studies have been inconsistent. Kendler and colleagues reported increases in NA (but no reductions in PA) after a depressive episode relative to predepression levels in two separate samples (Fanous, Neale, Aggen, & Kendler, 2007; Kendler et al., 1993); however, other studies have found that NA and PA do not change from before to after an MDE (e.g., Ormel, Oldehinkel, et al., 2004; Shea et al., 1996). Importantly, the studies reporting scarring used less stringent criteria for recovery and shorter follow-ups, suggesting that the findings may be due to residual symptoms and/or that the scars dissipate over time.

Twin studies provide a particularly useful approach to testing the common cause and precursor models. These studies indicate that there are substantial associations between the genetic liabilities for NA and MDD but only weak associations between the liabilities for PA and MDD (Fanous et al., 2007; Kendler et al., 1993; Kendler, Gatz, Gardner, & Pederson, 2006).

The most direct approach to testing the precursor and predisposition models is to conduct prospective studies of personality in never-depressed participants to determine whether traits predict the subsequent onset of depressive disorder. Several studies using large community samples have reported that higher levels of NA predict the onset of first lifetime MDEs (De Graaf, Bijl, Ravelli, Smit, & Vollebergh, 2002; Fanous et al., 2007; Kendler et al., 1993, 2006; Ormel, Oldhehinkel, et al., 2004). There is also evidence that low PA predicts the first onset of MDD (Kendler et al., 2006; Rorsman, Grasbeck,

Hagnell, Isberg, & Otterbeck, 1993), but it is much weaker and several studies have failed to find an association (Fanous et al., 2007; Hirschfeld et al., 1989; Kendler et al., 1993). However, these studies have not examined PA at the facet level or distinguished between the affective and interpersonal aspects of PA, and there is evidence that the former are much more strongly linked to depression than the latter (Watson & Naragon-Gainey, 2010).

Several prospective studies have examined whether stressful life events moderate or mediate the effects of personality on depression. Although not dispositive, such evidence is more central to the claims of the predisposition model than the common cause and precursor models. These studies indicate that life stress moderates the association between NA and depressive episodes and symptoms (Kendler, Kuhn, & Prescott, 2004; Ormel et al., 2001). In addition, Spinhoven et al. (2011) recently reported that experiencing fewer positive life events mediates the association between low PA and increased depressive symptoms.

Finally, to test the pathoplasty model, a number of studies have assessed personality during MDEs and followed the individuals to examine their course and outcome. This work indicates that higher NA and lower PA both predict a poorer course (Duggan, Lee, & Murray, 1990; Klein et al., 2011). Although these findings are consistent with the pathoplasty model, they cannot exclude the possibility that extreme traits are a marker for a more severe or etiologically distinct subgroup of depression (Klein et al., 2011).

Thus there is evidence supporting the concomitants, common cause, precursor, vulnerability, and pathoplasty models for NA and the pathoplasty, and to a lesser degree the precursor and vulnerability, models for PA. These models are not mutually exclusive, so it is conceivable that several are relevant for the same trait. However, it also is possible that some models are more applicable for some facets of NA and PA than others. Moreover, there also is evidence that the associations of NA with depression may be moderated by PA, as well as conscientiousness (Klein et al., 2011).

Disorders. Although there is a vast literature on the concurrent associations between PD and depressive disorders, fewer studies have attempted to test explanatory models of their relations. Most of these studies have focused on the question of whether PD has pathoplastic effects on the course and treatment of mood disorders. There is considerable evidence that comorbid PD is associated with a longer duration and greater risk of recurrence of MDEs (e.g., Grilo et al., 2005, 2010; Skodol et al., 2011). However, as discussed below, the literature on treatment response is less consistent. Recent meta-analyses have reached differing conclusions (Kool et al., 2005; Newton-Howes, Tyrer, & Johnson, 2006), and the evidence for an association appears to be weaker when more stringent methodological and statistical approaches are employed (De Bolle et al., 2011).

The literature exploring other models of the association between mood disorders and PD is much sparser. The relation of BPD to the mood disorders has received the greatest consideration. Both BPD and depressive disorders are defined, in part, by dysphoric affect and an increased risk for suicidal behavior, hence construct/content overlap is a concern. However, there is evidence that the association persists even when overlapping criteria are eliminated (Pepper et al., 1995). Moreover, there may be qualitative differences between the dysphoria experienced in MDD and BPD, with the former characterized by guilt and remorse and the latter by loneliness, anger, and a sense of inner "badness" (Silk, 2010).

A number of studies have examined whether BPD and depression have common causes by examining family history, biological correlates, and response to pharmacotherapy. This literature finds substantial overlap but also evidence of distinctiveness. Family studies indicate that there is an elevated rate of MDD and DYS in relatives of patients with BPD, even after controlling for comorbid depression in probands and comorbid BPD in the relatives (Zanarini, Barison, Frankenburg, Reich, & Hudson, 2009), suggesting the existence of shared familial risk factors. However, the data on whether the relatives of patients with MDD have increased rates of PD are inconsistent, although the relatives of patients with DYS without co-occurring BPD have an elevated risk of BPD (Riso et al., 1996).

Goodman, New, Triebwasser, Collins, and Siever (2010) recently reviewed the literature on neurobiological correlates of BPD and MDD. They concluded that whereas patients with MDD fail to suppress cortisol production after administration of dexamethasone, patients with BPD exhibit enhanced suppression. In contrast, both disorders are characterized by reduced serotonin neurotransmission. Structural and functional neuroimaging studies indicate that both conditions exhibit similar abnormalities in anterior cingulate cortex volume, amygdala reactivity to emotional stimuli, and

hippocampal volume. However, some studies have reported that MDD is characterized by increased, and BPD by diminished, anterior cingulate cortex reactivity to emotionally provocative stimuli. In addition, patients with MDD have abnormally high amygdala activity at rest, while patients with BPD appear to exhibit increased amygdala activation to a broader range of emotional stimuli.

MDD and BPD also differ on response to antidepressant medication. Although antidepressants can be helpful in managing some aspects of BPD, most core features of the disorder do not respond to pharmacotherapy (Mercer, Douglass, & Links, 2009; Soloff, 2000).

Finally, two studies have investigated the direction of the effects between depressive symptoms and BPD traits using prospective longitudinal designs (Gunderson et al., 2004; Klein & Schwartz, 2002). Both studies observed that BPD traits predicted depressive symptoms more strongly than depressive symptoms predicted BPD traits, which is consistent with the view that BPD may be a risk factor for depression. However, Klein and Schwartz (2002) also tested a model that included a temporally fixed common factor along with unique influences on both depression and BPD traits that provided an even better fit to the data. These data are consistent with some of the familial and neurobiological evidence mentioned earlier suggesting that BPD and depression are products of a combination of shared and distinct influences. As a next step in teasing apart the common and unique influences in depression and BPD, it may be useful to parse BPD into its component traits and test hypothesized causal models at this more specific level of analysis.

Implications for Clinical Practice

Assessment

Approaches. In clinical settings, personality assessment is helpful for identifying treatment goals and selecting interventions. Unfortunately, as noted above, this is complicated by the low concordance between different PD measures (Clark et al., 1997; Skodol, Oldham, Rosnick, Kellman, & Hyler, 1991).

A number of interviews have been designed to assess a range of features relevant to the diagnosis of PD (Zimmerman, 1994). Although PD is often assessed using unstructured interviews, semi-structured interview approaches have better interrater reliability (Widiger & Samuel, 2005). Existing semi-structured interviews that assess the full range of *DSM-IV* PDs include the Personality Disorder Interview-IV (PDI-IV; Widiger, Mangine, Corbitt, Ellis, & Thomas, 1995); the Diagnostic Interview for *DSM-IV* Personality Disorders (DIPD-IV; Zanarini, Frankenburg, Sickel, & Yong, 1996); the Structured Clinical Interview for *DSM-IV* Axis II Personality Disorders (SCID-II; First, Gibbon, Spitzer, Williams, & Benjamin, 1997); the Structured Interview for the *DSM-IV* Personality Disorders (SIDP-IV; Pfohl, Blum, & Zimmerman, 1997); and the International Personality Disorders Examination (Loranger, 1999), which assesses both *DSM-IV* and International Classification of Diseases diagnoses.

Most interviews take about 90 minutes to administer, whereas the PDI-IV can take up to 120 minutes and the SCID-II can take less than 60 minutes, particularly if the self-report screener is used. The format of these interviews varies: questions are grouped by topic (e.g., interpersonal relationships, employment) in the International Personality Disorders Examination and by diagnosis in the DIPD-IV and SCID-II; the PDI-IV and the SIDP-IV offer versions with each format. Empirical data do not support the use of a particular format (Skodol et al., 1991). Of these interviews, the IDPE, SIDP-IV, DIPD-IV, and SCID-II have the most empirical support.

Other interviews are designed to assess pathological personality traits. Most assess personality traits relevant to a single PD category, including the Diagnostic Interview for Borderline Patients–Revised (Zanarini, Gunderson, Frankenburg, & Chauncey, 1989), the Diagnostic Interview for Narcissism (Gunderson, Ronningstam, & Bodkin, 1990), and the Psychopathy Checklist–Revised (Hare, 1991), whereas the Personality Assessment Schedule (Tyrer, 1988) assesses traits across multiple domains. These interviews show adequate psychometric properties when used by trained raters. Because the target personality traits are assessed in far greater detail, these trait-focused interviews can take as much time to administer as the diagnostic interviews.

There is also a wide range of self-report assessments of PD and normal and abnormal personality traits. Examples include the Millon Clinical Multiaxial Inventory (Millon, Davis, & Millon, 1994) the Minnesota Multiphasic Personality Inventory–Personality Disorder Scales (Morey, Waugh, & Blashfield, 1985), the Personality Assessment Inventory (Morey, 1991), the NEO Personality Inventory (Costa & McCrae, 1992), the Schedule of Nonadaptive and Adaptive

Personality–2 (Clark, 1993; Clark et al., in press), the Temperament and Character Inventory (Cloninger, 1994), and the Dimensional Assessment of Personality Disorder Pathology (Livesley, 2006). In addition, Krueger and colleagues (2011) recently developed the PID-5, mentioned earlier, based on a maladaptive personality trait model proposed by the *DSM-5* workgroup. Self-report assessments can be particularly useful as screening instruments given their low cost.

Informant reports can improve the quality of the assessment, as multiple sources of information provide more comprehensive data than a single source (Tyrer & Ferguson, 1987; Zimmerman, 1994). In addition, reports by individuals with personality difficulties may be inaccurate (Klonsky, Oltmanns, & Turkheimer, 2002), although perhaps no more so than those without personality pathology (Ready & Clark, 2002). Most existing interviews can be adjusted for administration with informants, and some self-report instruments have an informant version (e.g., Schedule of Nonadaptive and Adaptive Personality–Other Rating Form, Harlan & Clark, 1999; NEO Personality Inventory Form R, Costa & McCrae, 1992). Despite the potential value of including informant reports in assessment of PD and traits, self-report is still considered necessary because informants typically cannot report on the thoughts and feelings of the target individual. Moreover, there is only modest agreement between self- and informant report (Clifton, Turkheimer, & Oltmanns, 2005; Klonsky et al., 2002; Riso, Klein, Anderson, Ouimette, & Lizardi, 1994; Walters, Moran, Choudhury, Lee, & Mann, 2004). However, both sources of data make independent contributions in predicting subsequent outcome such as depressive symptoms and functional impairment (Klein, 2003; Ready, Watson, & Clark, 2002; Oltmanns & Turkheimer, 2006).

Effects of personality and depressive disorders on assessment. The presence of personality pathology may complicate the assessment of depression and vice versa. As discussed earlier, state effects of depression on personality refers to the finding that individuals who are currently depressed tend to overreport symptoms of personality pathology (De Fruyt et al., 2006; Farabaugh, Mischoulon, Fava, Guyker, & Alpert, 2004). Stuart, Simons, Thase, and Pilkonis (1992) found that, posttreatment, remitted depressed patients no longer met criteria for PD that was diagnosed at intake (although it is possible that treatment addressed both disorders). However, some investigators have reported that semi-structured diagnostic interviews can reduce the effects of the depressed state on reporting of PD features (Loranger et al., 1991). Other approaches to reduce mood state effects include using informants and gathering a detailed history of the individual (Widiger & Chaynes, 2003).

There also is evidence that individuals with personality pathology overreport depressive symptoms. For example, in studies comparing clinician-rated depressive symptoms to self-report, individuals with BPD with and without MDD report more depressive symptoms in self-reports relative to clinician ratings (Silk, 2010). However, this may be due to underlying personality characteristics rather than specific to PD per se, as individuals with higher Neuroticism, lower Extraversion, and lower Agreeableness—all common personality deviations in PD—showed greater self–clinician discrepancies (Enns, Larsen, & Cox, 2000). Given the impact of depressive symptoms and personality characteristics on assessment, as well as the complexity of both depression and personality, it is important to conduct a comprehensive assessment that integrates self- and informant report, clinician observation, and available documentation (e.g., treatment records).

Treatment

Many clinical researchers have been interested in the role of personality and PD in the treatment of depressive disorders (an aspect of the pathoplasty model discussed earlier). Important questions include whether (a) personality predicts treatment response, (b) information about personality can aid in treatment selection, (c) treatment influences personality, and (d) changes in personality mediate the effects of treatment. In this section, we first review the evidence regarding the role of personality traits in the treatment of depressive disorders and then consider the role of PD.

There is substantial evidence that individuals with lower NA have better responses to various forms of treatment (Kennedy, Farvolden, Cohen, Bagby, & Costa, 2005; Mulder, 2002; Tang et al., 2009). There also is evidence that higher PA is associated with a better response, although the findings are somewhat less consistent (Kennedy et al., 2005; Tang et al., 2009). Other traits have been less studied. However, in one of the largest studies conducted to date, Quilty, De Fruyt, et al. (2008) examined the ability of the FFM traits to predict response to combined pharmacotherapy and psychotherapy in depressed outpatients. They found that higher NA

and lower conscientiousness independently predicted poorer outcomes and that both effects were moderated by PA, such that patients with high NA and low PA and patients with low conscientiousness and low PA were least likely to respond. Few studies have examined facets of these higher order trait dimensions, but preliminary evidence suggests that lower order traits can add substantially to the prediction of treatment response (Bagby et al., 2008). Further work is needed to delineate the mechanisms underlying the personality–treatment response association. For example, traits could predict poorer response because they are indicative of a more severe form of depression or because they moderate the effects of stress during treatment (Bulmash, Harkness, Stewart, & Bagby, 2009).

Most efficacious treatments for depression have only modest effects, hence it is often necessary to try multiple treatments before obtaining a response. If personality traits predict response to some forms of intervention but not others, this would make a valuable contribution to treatment selection (i.e., "personalized treatment"). Although there has been little research on this issue, there are suggestions that personality may predict differential response to treatment. Thus Bagby et al. (2008) reported that patients high on NA or low on some facets of Agreeableness responded better to antidepressant medication than psychotherapy. As discussed subsequently, there also is some evidence of differential treatment response in depressed patients with comorbid PD.

A number of studies have reported that the pharmacological and psychosocial interventions that are effective for depression also influence personality, for example reducing levels of NA and increasing levels of PA (e.g., De Fruyt et al., 2006; Quilty, De Fruyt, et al., 2008; Zinbarg, Uliaszek, & Adler, 2008). These changes do not appear to be simply concomitants of improvement in mood symptoms, as several studies have found that treatment-related changes in personality are not fully accounted for by reductions in depression (De Fruyt et al., 2006; Quilty, Meusel, et al., 2008; Tang et al., 2009).

If treatment-related changes in traits cannot be attributed to amelioration of symptoms, it is conceivable that change in personality *mediates* the effects of treatment on depression. Quilty, Meusel, et al. (2008) tested a mediation model and found that NA mediated the effects of pharmacotherapy in reducing depressive symptoms. Unfortunately, both NA and MDD were assessed only pre- and post-treatment, so it is unknown whether these results reflect an actual causal effect in which change in NA precedes change in depressive symptoms. If evidence of mediation is confirmed, then further research will be needed to identify the mechanisms that are responsible. For example, changes in traits might have a direct impact on symptoms, or this effect may be mediated by other processes, such as improving treatment compliance or the therapeutic alliance.

Studies of the role of PD in the treatment of depression have been limited to the prediction of treatment response. As noted earlier, the findings from this work have been less consistent than the research on traits, and meta-analyses have reached opposing conclusions (Kool et al., 2005; Newton-Howes et al., 2006). However, it is noteworthy that the evidence for an association appears to be somewhat weaker in studies using more stringent methodological and statistical approaches (De Bolle et al., 2011; Mulder, 2002).

It is conceivable that the weak or absent effects may be the result of aggregating across different PDs, different trait dimensions that constitute PD, or different interventions. In particular, there are suggestions that PD may have a greater impact on response to some treatments than others. For example, Fournier et al. (2008) reported that depressed patients with comorbid PD responded better to pharmacotherapy than cognitive therapy, while depressed patients without PD responded better to cognitive therapy than to pharmacotherapy. In addition, Joyce et al. (2007) found that in patients with MDD, comorbid PD predicted a better response to cognitive therapy than to interpersonal therapy. While these findings require confirmation, they raise the possibility that depressed patients with comorbid PD may respond better to more structured interventions (Mulder, 2011).

Summary and Conclusions

In summary, there are high rates of comorbidity between depressive disorders and PD, although rates vary substantially across studies and there is also variability regarding which specific types of PD are most common in depressed individuals. A somewhat more consistent picture emerges for the covariation of depression and the major personality trait dimensions. Depressive disorders exhibit large associations with NA and more moderate links with PA and conscientiousness/disinhibition. However, as the data presented in Table 13.1 indicate, finer-grained analyses at the facet level reveal an even more differentiated pattern of associations.

Hence, future work should be conducted at both the trait and facet levels. Moreover, like PD, depressive disorders are heterogeneous. Thus it is important to explore different subtypes and dimensions of depression in future research on PD comorbidity.

Conceptually and empirically disentangling the relations of depression and PD continues to be challenging, as depression is associated with personality traits even in the absence of PD. Proposals to revise *DSM-5* place will place greater emphasis on unidimensional traits, which will hopefully produce more consistent and interpretable patterns of comorbidity with PD. They also define PD independently of traits (i.e., disturbances in self- and interpersonal functioning), which may help to distinguish PD–depression comorbidity from trait–depression covariation, although this may not be entirely straightforward, as depression is also characterized by maladaptive self-beliefs and interpersonal difficulties.

Our understanding of the processes responsible for the associations of PD and traits with depressive disorders is still quite limited. There is support for multiple explanations, including the concomitants, common cause, precursor, vulnerability, and pathoplasty models. Moreover, it is possible that different models apply not only to different broad trait dimensions but also to different facets within a higher order trait. The work in this area has focused almost exclusively on NA and PA. It is important to extend this research to conscientiousness (Kotov et al., 2010), examine personality at the facet level, and consider the possibility that some traits may moderate the effects of other traits. For example, PA and conscientiousness may exacerbate or attenuate the effects of NA (Klein et al., 2011). Finally, although personality traits and PD are both moderately stable (and personality likely somewhat more so; Clark, 2007), they are influenced by developmental processes and environmental factors. Thus it is important to consider the complex personality–environment transactions that can strengthen or attenuate personality trajectories and predispositions for depressive disorders (Ormel et al., 2001).

Irrespective of the nature of the links between depression and PD, personality traits and disorders have important clinical implications for the assessment and treatment of depression. There is evidence that the depressed state influences the assessment of personality and PD influences the assessment of depressive symptoms. In addition, high NA and low PA are associated with a poorer treatment response, although the effects of categorically diagnosed PD on treatment are mixed. The mechanisms underlying personality–treatment response association are unclear, and further work is needed in this area. However, there are intriguing suggestions that NA may mediate treatment response in MDD (Quilty, Meusel, et al., 2008). In addition, there is suggestive evidence that personality traits and disorders may predict differential response to specific treatments (e.g., Bagby et al., 2008). Given the modest efficacy of existing antidepressant pharmacotherapies and psychotherapies, and the lack of differential treatment predictors to aid treatment selection, further research to confirm and extend these findings is critical.

Future Research Directions

As discussed above, future research on the comorbidity between depression and PD should address the following issues. First, it is important to examine the associations between depression and personality pathology at both the trait and facet levels, as well as with different subtypes and dimensions of depression. Second, use of the proposed *DSM-5* conceptualization of PD, which emphasizes unidimensional traits, should help to identify more consistent and interpretable patterns of comorbidity. Third, work on the association of personality traits and depression should examine conscientiousness, in addition to NA and PA, and interactions between traits should be considered. Fourth, it will be important to conduct longitudinal studies to examine the complex personality–environment transactions that contribute to particular personality trajectories and risk for depressive disorders. Finally, further work is needed to clarify the mechanisms underlying the association between personality and treatment response, confirm initial findings on personality trait mediation of treatment, and examine trait by treatment interactions to facilitate optimal matching of patients to specific interventions.

Note

1. Although the *DSM-5* lists several facets in two domains based on their empirical relations (e.g., Depressivity and Suspiciousness facets reflect both the Negative Affectivity and Detachment domains), we assigned each facet to a primary domain for our analyses.

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CHAPTER

14 Sexual Dysfunction

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Abstract

Sexual dysfunction covers a range of disturbances in sexual response affecting desire, arousal, and orgasm or involving pain with sexual activity. Depression and sexual dysfunction have long been known as comorbid conditions; however, some research suggests that depressed mood may not always be associated with specific sexual dysfunctions. Associations between sexual dysfunction and depression appears bidirectional, such that either one of these conditions may trigger or worsen the other, while improvement in one may also improve the other. This chapter examines the complex relationship between depression and male and female sexual dysfunctions. We explore the classification and prevalence of sexual dysfunction, the known interconnections involving neurobiology, and psychological issues. Finally, we summarize the core principles of evaluation and treatment of common sexual dysfunctions, particularly in the context of depressive illness.

Key Words: depression, sexual dysfunction, desire, arousal, orgasm, erectile dysfunction, dyspareunia

Introduction

Sexual dysfunction encompasses a range of disturbances in sexual response affecting desire, arousal, and orgasm or involving pain with sexual activity. These problems are usually considered disorders or dysfunctions only when resulting in distress for the individual, though this varies with classification system, particularly for women (Basson et al., 2000; DeRogatis & Burnett, 2008). Depression and sexual dysfunction have long been observed as comorbid conditions. Loss of pleasure is a *Diagnostic and Statistical Manual for Mental Disorders* (fourth edition [*DSM-IV*]; American Psychiatric Association, 1994) criterion for major depressive disorder (MDD), and, unsurprisingly, reduced sexual desire is the most common sexual dysfunction among patients with untreated depression (American Psychiatric Association, 2000; Bonierbale & Tignol, 2003; Williams & Reynolds, 2006). However, impaired erection/arousal, orgasm, and sexual pain disorders (in women) are also increased in those with depression (Kennedy & Rizvi, 2009).

The association between sexual dysfunction and depression appears bidirectional, such that either one of these conditions may trigger or worsen the other, while improvement in one may also improve the other (Althof & Leiblum, 2004). For example, erectile dysfunction (ED) may follow the onset of depression, or, alternatively, men may develop secondary depression associated with ED (Araujo, Durante, Feldman, Goldstein, & McKinlay, 1998; Kennedy & Rizvi, 2009; Seidman & Roose, 2000). Depression may also mediate systemic diseases, such as cardiovascular disease, which then increases the risk for sexual dysfunction, such as ED (Seidman & Roose, 2000).

This chapter will examine the complex relationship between depression and male and female sexual dysfunctions. First, we explore the classification and prevalence of sexual dysfunction in the

general population then specifically address sexual dysfunction prevalence in the context of depression. Next, we review the neurobiology mediating both sexual response and mood. Finally, we summarize the core principles of the medical and psychological evaluation and treatment of common sexual dysfunctions, particularly in the context of depressive illness.

Classification and Prevalence

Determining the prevalence of sexual dysfunction is highly dependent on the classification or diagnostic criteria, as well as the sample population (Lewis et al., 2004). *DSM-IV* remains the most widely used classification system and categorizes sexual problems into desire, arousal, orgasm, and pain disorders, with a variety of modifiers (global vs. situational, lifelong vs. acquired). The *DSM-IV* system emphasizes psychological over medical causes (or classifying the disorder as a combined subtype), persistent or recurrent symptoms, and the A and B definition categories separate the symptoms of the sexual dysfunction from the associated distress (Hatzimouratidis & Hatzichristou, 2007).

The International Consultation on Sexual Medicine classifications (Basson et al., 2000; Lewis et al., 2004), developed in collaboration between the International Consultation for Urological Diseases and the major sexual medicine and urological associations, preserves the same four categories of dysfunction as *DSM-IV* but does not distinguish between psychological and organic causes. According to the International Consultation, impaired sexual desire or response may be reactions to problems in sexual relationships or other intrapersonal factors and different sexual dysfunctions may be interrelated (Hatzimouratidis & Hatzichristou, 2007). While the *DSM-IV* and International Consultation classifications are structurally similar, the content reflects these different approaches. In general, *DSM-IV* tends to condense dysfunction into broader categories from which other, usually organic, causes of the symptoms are excluded. The International Consultation system, in contrast, has more subcategories and does not always distinguish between biological and psychological mechanisms. Unlike *DSM-IV*, the International Consultation system also accounts for the responsive nature of sexual desire in many women, as well as distinguishing between subjective and genital arousal dysfunction. Finally, individual professional societies may have varying diagnostic criteria for specific conditions, such as ED or premature ejaculation (PE).

An evidence-based literature review of the prevalence of sexual dysfunctions was conducted as part of the Second International Consultation on Sexual Dysfunctions (Lewis et al., 2010) and provides an excellent summary of the worldwide data and its limitations. For women, the prevalence of markedly lower sexual interest varies between 17% and 55% and tends to increase with age. Generally, arousal and lubrication problems are prevalent in 8% to 15% of women, although some studies report as high as 28% in sexually active women (Lewis et al., 2010). With age, particularly age greater than 50 years, lubrication issues become more prevalent; this increase is likely due to menopausal loss of vaginal estrogen rather than presence of an arousal disorder. Prevalence of orgasmic dysfunction in women is highly variable, ranging from 16% to 25% in several studies; however, a group of Scandinavian researchers reported more than 80% of all sexually active women age 18 to 74 years experienced orgasmic dysfunction (Fugl-Meyer & Sjögren Fugl-Meyer, 1999; Öberg, Fugl-Meyer, & Fugl-Meyer, 2004). Studies indicate the prevalence of significant dyspareunia ranges from 14% to 27% (Lewis et al., 2010). Of note, prevalence studies of female sexual dysfunction may deliberately exclude dyspareunia, as did a large 2008 U.S. study (Shifren, Monz, Russo, Segreti, & Johannes, 2008), limiting data in this area. In addition, some have suggested sexual pain disorders in women may be better understood in the context of pain syndromes rather than categorized with the sexual dysfunctions (Binik, 2005).

Issues of low sexual desire are not well studied in men, but prevalence appear to be about 8% to 18%, with some increase with age over 60 years (Lewis et al., 2010). Conversely, ED has the largest evidence base to assess prevalence yet shows wide variation likely based on how information was collected, the way the population was sampled, the instruments utilized, and how ED was defined in the various studies. Nonetheless, ED is clearly age dependent, with prevalence of 1% to 10% up to the age of 40, 2% to 15% from 40 to 49, 15% to 30% from 50 to 59, 20% to 40% from 60 to 69, and anywhere from 50% to 100% for men in their 70s and 80s (Lewis et al., 2010). The prevalence for early (premature) ejaculation varies depending on definition and population sampled and ranges from 8% to 30%. Studies of delayed ejaculation and orgasmic difficulties in men are relatively few, but prevalence appears to be 1% to 10% and 12% to 19%, respectively (Lewis et al., 2010).

Associations Between Depression and Sexual Function

In general, this literature is difficult to summarize as there are a variety of approaches for defining and measuring sexual dysfunctions and depression, respectively. Some researchers have measured level of symptoms while others have categorized individuals based on diagnostic status using various diagnostic systems discussed earlier. To this end, participants have engaged in clinical interviews and/or have been asked to complete self-report measures of sexual problems and depressive symptoms. Comorbidity of sexual dysfunctions and MDD can be determined only when individuals complete clinical interviews by trained clinicians using diagnostic criteria to determine diagnoses. Unfortunately, few studies have employed such methodology, which requires a significant commitment of contact time between clinicians and research participants. Survey studies, in contrast, require less time of participants and typically include a larger sample size. In discussing the depression and sexual dysfunctions comorbidity literature, we include research describing participants' level of symptomatology as well as research classifying participants based on their diagnostic status. Only those studies describing findings in terms of difficulties with phases of sexual response cycle (i.e., desire/interest, arousal, orgasmic function, ejaculatory function) and specifying results for men and women, respectively, are included here. Sexual pain in women is included in a separate section.

Studies reporting results only in terms of participants' sexual satisfaction, pleasure, or distress are not included. Further, findings based on survey instruments (i.e., symptoms) are distinguished from research in which interviews were undertaken to determine diagnostic status in terms of sexual and/or depressive disorders. Only statistically significant odds ratios (*OR*) are included. While we have identified many studies focusing on depression and sexual functioning, a comprehensive literature review is outside the scope of this chapter.

Men

Survey studies. Analyses of survey data collected from a large, representative sample of older adults in the U.S. population indicated that depression was associated with sexual problems in men after controlling for demographic factors. For men, depressive symptoms were related to increased risk for lack of interest (*OR* = 1.4), trouble maintaining erection (*OR* = 1.6), and inability to achieve orgasm (*OR* = 1.4). However, depressive symptoms were not related to problems with early climax (Laumann, Das, & Waite, 2008). The specific problem of ED has been the subject of survey research across the world. Population-based studies conducted in Japan and Nigeria have found relationships between increased ED and severity of depressive symptoms (Okulate, Olayinka, & Dogunro, 2003; Sugimori et al., 2005). An online survey of adult men in the Middle East found increased risk for erectile problems (*OR* = 3.55) in men self-identified as having depression; however, the authors provided no information on risk after adjustments for confounding demographic, medical, or other variables (Shaeer & Shaeer, 2011). A study of 40- to 70-year-old men living in Brazil, Italy, Japan, and Malaysia found that men with elevated symptoms of depression also had increased risk for problems with ED after controlling for relevant demographic and medical variables (adjusted *OR* = 1.81; Nicolosi, Moreira, Villa, & Glasser, 2004). A cross-sectional sample representative of the population in the Boston area included the same age range and also found increased risk for ED (*OR* = 1.82) in men with elevated symptoms of depression after controlling for confounding variables (Araujo et al., 1998). However, not all research has supported the relationship between ED and depressive symptoms. A survey study of outpatients recruited from general medical practices in Pennsylvania failed to find an association between symptoms of depression and moderate or complete ED (Kantor, Bilker, Glasser, & Margolis, 2002). Also, a survey of younger Brazilian men (18 to 40 years old) found no link between erectile problems and depression (Martins & Abdo, 2010).

ED and PE have a high comorbidity rate (Jannini, Lombardo, & Lenzi, 2005). A large online survey study including men in the United States, Germany, and Italy found that men identified as having PE were significantly more likely to report problems with depression than men without PE (20.4% vs. 12.4%), and when men with comorbid erection difficulties were excluded from analyses, the difference remained significant (Porst et al., 2007). An online study of Korean men also found that depression levels were significantly higher in men meeting study criteria for PE versus men who did not meet criteria. Again, differences remained significant after men with erection problems were excluded from analyses (Son, Song, Lee, & Paick, 2011).

Studies of MDD. Studies of men diagnosed with MDD and including measures of sexual functioning are few, and the significance of findings is

unclear. Two studies finding associations between depression and sexual function reported problems with decreased desire (42%), erection (19%–46%), and ejaculation/orgasm (12%–22%). These studies included a *washout period* for individuals taking antidepressant medication and in this way controlled for the effects of medications on sexual functioning (Kennedy, Dickens, Eisfeld, & Bagby, 1999; Zajecka et al., 2002). However, without a control group, the significance of these findings cannot be determined. Several studies that have included control groups of nondepressed men have yielded mixed results. An early, small-scale study found that men diagnosed with a depressive episode had significantly lower sexual interest ratings than nondepressed men (Howell et al., 1987). A study conducted in Switzerland compared individuals diagnosed with depression (major depression, dysthymia, and recurrent brief depression) with a nondepressed group and found more problems with low libido in depressed men (25.7% vs. 11.1%); however, the significance of this finding was not reported (Angst, 1998). A sample of male outpatients diagnosed with MDD was compared to a nondepressed control group prior to initiating treatment for depression. No significant differences in sexual desire were found between groups. Unfortunately, study measures did not include erectile and ejaculatory problems (Nofzinger et al., 1993).

Studies of sexual dysfunctions. Another research design investigating links between depression and sexual dysfunction begins with identifying individuals with a sexual dysfunction and then examines the rates of depression in the identified sample. One such study investigated depression in individuals with *inhibited sexual desire disorders* as defined in the *Diagnostic and Statistical Manual of Mental Disorder* (third edition [*DSM-III*]; American Psychiatric Association, 1980). Although none of the men met criteria for a current diagnosis of depression, men diagnosed with inhibited desire also had higher levels of depressive symptoms when compared to a control group of men without any sexual disorder. Moreover, men with inhibited desire also had a significantly higher lifetime prevalence rate of depressive disorder when compared to the control group (Schreiner-Engel & Schiavi, 1986). A later study including Dutch men who were diagnosed with hypoactive sexual desire disorder (HSDD), ED or PE did not find significantly higher rates of comorbid MDD in comparison with MDD rates in the general Dutch population. When history of MDD was considered, no significant differences were found in comparison with the general population (van Lankveld & Grotjohann, 2000). An online study of Canadian men incorporated a follow-up interview to identify men with PE using *DSM-III* diagnostic criteria. More men with PE than men without PE self-identified as having current depression (18% vs. 7%); however, the statistical significance of this difference was not reported (Brock et al., 2009).

Summary. Taken together, studies including survey methods and those studies including diagnosis of depressive or sexual disorders suggest correlations between male sexual dysfunction and depressive symptoms; however, it is important to note that not all studies support these associations. Some data support correlations between desire problems and depressive symptoms. However, prevalence rates of comorbid or lifetime history of MDD may not be higher in men with diagnosed desire disorders than in men with no desire problems. Much of the research supporting links between ED and depression has been based on survey studies where clinical diagnosis of ED or depression has not been ascertained. Notably, these studies have spanned the world, including the Middle East, Asia, Europe, Africa, as well as North and South America. Research recruitment strategies have ranged from recruiting participants from public places and social networking sites to more traditional approaches such as recruiting participants from medical clinics. Given the range of sampling techniques and methods for defining the relevant conditions, the mixed findings are not surprising: Risk for erectile problems in men with depressive symptoms ranged from none to a reported *OR* of 3.55. We found only one population-based study using interview methods to determine clinical diagnosis of sexual dysfunction and MDD, respectively, and these researchers reported no increased risk for comorbid MDD in men with ED (van Lankveld & Grotjohann, 2000). Studies examining associations between PE and MDD also yielded mixed findings. Survey studies employing online recruitment methods and including international samples have found increased depressed mood in men with PE; however, a study using a rigorous interviewing method to diagnose individuals did not find a link between PE and MDD. Few studies have investigated links between sexual pain and depression in men. In summary, rates of comorbid diagnosis of MDD and any of the male sexual disorders are unknown. The few studies that included diagnostic assessment for both male sexual disorders and MDD have found no comorbid

cases. Thus these rates will need to be determined based on future studies that include clinical assessment of both MDD and sexual dysfunctions.

Women

Survey studies. Results of surveys asking women to report on their depressive symptoms and sexual problems suggest some associations between these difficulties. A population-based study conducted in England focused on a wide age range (18 to 75 years) and found strong relationships between elevated depressive symptoms and arousal problems, orgasmic problems, and vaginal dryness; however, whether or not these associations may have been confounded by other variables was not addressed (Dunn, Croft, & Hackett, 1999). Another population-based study, this one including Australian women age 20 to 70 years, also found an association between elevated symptoms of depression and self-reported sexual problems. After adjusting for relevant demographic and relationship factors, women with elevated symptoms of depression had a greater risk for low genital arousal (*OR* = 2.5) but no significantly increased risk for low desire or orgasmic problems (Hayes et al., 2008). A U.S. population-based study including sexually active women between the ages of 57 and 85 years asked participants to identify areas of difficulty with sexual functioning and also to rate their level of depressive symptoms. After controlling for relevant variables, depressive problems were associated with increased lack of interest (*OR* = 1.5), inability to achieve orgasm (*OR* = 1.7), and lack of pleasure (*OR* = 1.8). However, depression was not significantly associated with increased risk for difficulty with lubrication (Laumann et al., 2008). Another U.S., population-based study of women's sexual function included a wider age range, 18 years and older. Prevalence of distressing sexual problems was calculated for the overall sample and then for the subsample not endorsing indicators of depression (Johannes et al., 2009). The prevalence rates of sexual problems were lower when women identified as *depressed* were not included in the analyses: low desire 6.3% (overall 10%), arousal problems 3.3% (overall 5.4%), orgasm problems 2.8% (overall 4.7%). While the strength of these survey studies includes having large, population-based samples, diagnostic status with regard to depression or sexual disorder was not established.

Studies of MDD. Four studies recruiting women diagnosed with an episode of major depression included an initial washout period or excluded women taking psychiatric medications to rule out effects of antidepressant medications on sexual functioning. In one sample of women diagnosed with MDD (*N* = 79), women reported low sexual interest (50%), low arousal (50%), problems with lubrication (40%), and orgasmic problems (15%; Kennedy et al., 1999). A small-scale intervention study for women with a current diagnosis of MDD who had experienced at least one previous depressive episode described baseline findings: 31% reported no sexual interest, 40.9% reported lubrication problems, and 37.9% reported dissatisfaction with orgasmic ability (Cyranowski, Frank, Cherry, Houck, & Kupfer, 2004). In a larger sample of women with MDD, 18% reported inadequate swelling or vaginal lubrication during arousal, 21% experienced inability to achieve orgasm, and 19% reported decreased orgasmic intensity (Zajecka et al., 2002). Unfortunately, none of these three studies included a nondepressed control group, thus the significance of these findings are unknown.

The largest study including clinical assessment of MDD that we identified was conducted by Fabre and Smith (2012) and included participants recruited at multiple sites. Methods and data collected at these sites varied. Sexual function was measured using the Derogatis Inventory of Sexual Function (DISF), which allowed for comparison of study women with established DISF population norms. Not all women completed the DISF, and not all women engaged in a clinical assessment of sexual functioning. Of the 904 women completing the clinical assessment, *DSM-IV* diagnostic status was reported as follows: 17.7% HSDD, 3.2% sexual aversion disorder, 5.6% arousal disorder, 7.5% orgasmic disorder. DISF subscale scores indicated that study women had poor sexual functioning: sexual desire (16th percentile), sexual arousal (22nd percentile), and orgasmic function (4th percentile). However, it should be noted that arousal scores were still within the normative range and desire scores were within the lower limit of the normal population range (i.e. within one standard deviation). Orgasmic function was most affected, almost three standard deviations from the norm. DISF total scores (5th percentile) also indicated poor sexual functioning, close to three standard deviations below the norm.

Studies of sexual dysfunctions. While the findings just discussed describe sexual functioning in the context of a diagnosed depressive episode, other research has focused on recruiting women who are experiencing a sexual dysfunction and then examining their depression levels. These studies have largely

focused on hypoactive desire. A study including Dutch women diagnosed with a sexual dysfunction compared incidence of depression in these women with incidence of depression in the general population. Incidence of comorbid MDD in women with HSDD or orgasmic disorder was not significantly higher than incidence of MDD for women in the Dutch population. Diagnosis of arousal disorder was not evaluated in this study. When lifetime diagnosis of MDD was considered, women with HSDD (32.5%) had a significantly higher proportion of affected individuals when compared to women in the general population (20.1%; van Lankveld & Grotjohann, 2000). A small study including women diagnosed with inhibited sexual desire (N = 24) based on *DSM-III* criteria found no current cases of MDD. However, when lifetime history of MDD was considered, prevalence rates were significantly higher for women with inhibited desire (33%) than for the control group of women without a sexual disorder (7%; Schreiner-Engel & Schiavi, 1986). A later study including only women diagnosed with HSDD based on *DSM-IV* criteria classified 35% as depressed based on a self-report measure. Women completed multiple measures reflecting their sexual desire and excitement. When relationships between sexual functioning measures and depression levels were analyzed, findings were mixed with only some measures of sexual desire and excitement significantly lower in the more depressed group (McVey, 1997). A report of baseline data obtained from a large registry of premenopausal women with HSDD has recently been published (Clayton et al., 2012). All women were diagnosed with HSDD using *DSM-IV* criteria, and 34.4% were identified as depressed (i.e., having current symptoms of depression or undergoing current treatment for depression). Because the study did not include a clinical assessment for depression, cases of MDD were unknown. Within the registry women identified as depressed had poorer overall sexual functioning than women without current indicators of depression.

Studies of sexual pain disorders. A study of older women in the United States found that depressed mood increased risk for experiencing pain during sex (*OR* = 1.4; Laumann et al., 2008). In a Dutch study, women with dyspareunia had significantly higher incidence of MDD (15.6%) when compared to incidence of MDD in the general population (3.4%). A similar pattern was evident when comparing lifetime diagnosis of MDD: 43.8% for women with dyspareunia versus 20.1% for women in the general population (van Lankveld & Grotjohann, 2000). A study of women diagnosed with vulvodynia ($N = 50$) found that higher depression ratings were related to some measures of pain severity and overall sexual functioning; however, depression was not significantly related to other measures of pain including the Pain subscale of the Female Sexual Function Index (FSFI). Diagnostic interviews resulted in current diagnosis of MDD in 18% of the study sample while 46% had a lifetime diagnosis of MDD. Due to lack of a comparison nondepressed group, the statistical significance of these findings could not be ascertained (Masheb, Kerns, Lozano, Minkin, & Richman, 2009).

While these studies suggest some relationships between sexual pain and depressed mood, results of studies including women experiencing a range of sexual pain conditions (e.g., vaginismus, vulvar vestibulitis, and vulvodynia) are mixed (Meana, 2009). One reason for the mixed findings may be that studies recruit from different populations: women seeking specialty care for these conditions and women who have these same pain conditions but who are not treatment seeking (Green & Hetherton, 2005).

Summary. Many studies of sexual function and depression in women have included focus on the sexual desire/interest phase of the sexual response cycle. While data are mixed, some studies have found significant associations between severity of depressive symptoms and increasing problems with sexual interest or desire. In samples of women diagnosed with MDD, desire or interest problems ranged from 17% to 50%. As previously discussed, estimates of sexual interest problems in women in the general population have ranged from 17% to 55%. Using these estimates as a comparison, one cannot conclude that desire problems are higher in women with MDD; however, such comparisons should be undertaken with considerable caution due to differences in study recruitment and methodology. Only two studies used diagnostic criteria to identify women with desire disorder and MDD and also included an appropriate reference comparison group (Schreiner-Engel & Schiavi, 1986; van Lankveld & Grotjohann, 2000). Both studies reported similar results suggesting women with HSDD are not at higher risk for experiencing an episode of depression. However, some evidence suggests that women with HSDD have higher lifetime prevalence of MDD. These data will need to be replicated, and the hypothesis that history of depression increases risk for developing HSDD should be explored. Unfortunately, few studies included

measures of arousal and lubrication problems, and it would be premature to draw any conclusions about links between arousal problems and depression at this time. The studies including women diagnosed with MDD have reported incidence of orgasmic problems from 7.9% to 37.9% using a variety of sexual functioning measures. The lowest rate was reported in a study in which a diagnosis of orgasmic disorder was established while the highest rate was reported in a study that defined orgasmic problem as dissatisfaction with orgasmic ability. Again these data emphasize the importance of how researchers define sexual dysfunction and point to the need for agreement in definition and measurement instruments so that research can be replicated and data can be analyzed across studies.

These studies are cross-sectional, thus conclusions regarding whether sexual dysfunctions cause depression or vice versa cannot be made. Longitudinal studies are required to provide more information on the development of sexual dysfunction in the context of depression or alternatively on the development of depression in the context of sexual dysfunction. Indeed, a large registry of women with HSDD has been established, and, as these women are being followed, valuable information on links between depression and sexual functioning will be revealed (Clayton et al., 2012). While none of the studies discussed here included measures of hormones or neurotransmitters, measurement of these biochemical variables as well as other psychosocial factors may need to be included to develop models adequate for explaining the complex interplay between depression and sexual dysfunction.

The Role of Neurotransmitters in Mood and Sexual Response

Mood and sexual function share a number of neurobiological systems, involving both hormonal and neurological transmitters that act synergistically as well as antagonistically (Meston & Frohlich, 2000; Michael & O'Keane, 2000). An individual neurotransmitter can have multiple receptor sites; thus the same transmitter can actually have contradictory effects, depending on which receptor is being stimulated. These systems operate at numerous levels in the body, including the hypothalamus-pituitary axis, brain, autonomic nervous system, blood vessels, and intestinal tract.

Hypothalamus and Pituitary (HPG) Axis

The gonadotropin releasing hormone (GnRH), synthesized in the hypothalamus, regulates the production and secretion of luteinizing hormone (LH) and follicle stimulating hormone (FSH) by the anterior pituitary. LH and FSH stimulate the production of androgens (such as testosterone), estrogens, and progestins. HPG axis dysfunction can result in hypogonadism with low sex steroid levels, while depression itself has been associated with HPG axis changes (Michael & O'Keane, 2000). A clinically significant decrease in androgens or estrogen has been associated with decreased mood, though neither hypogonadal men nor postmenopausal women invariably suffer from depression (Michael & O'Keane, 2000). The relationship between testosterone and sexual function in both men and women is complex, and adequate sexual function is possible with relatively low levels of androgens (Meston & Frohlich, 2000). Prolactin and oxytocin are also produced by the pituitary. Prolactin may inhibit while oxytocin may enhance sexual receptivity in women (Clayton, 2007), but their roles in depression are less clear (Pfaus, 2009).

Neurotransmitters

Deficiency of one or another monoamines—primarily norepinephrine, serotonin, and dopamine—is a significant factor in the physiopathology of depression. Increased understanding of the effects of monoamines on mood has led to the development of several generations of antidepressant medications, including selective serotonin reuptake inhibitors (SSRIs; Silverstone, 1992). Widespread use of these medications— and their side effects—has illuminated the role of monoamine neurotransmitters in sexual response as well.

Dopamine. Reduced release of dopamine appears to play a strong role in at least the anhedonic subtype of depression and is related to the inability to experience pleasure (Dunlop & Nemeroff, 2007). Both of dopamine's two main receptors appear to activate sexual responses, including libido and erection. Drugs such as bromocriptine, bupropion, and cocaine increase available dopamine, facilitate erections, delay ejaculation, and increase libido and arousal. Drugs that block or decrease available dopamine, such as antipsychotics, impair erections and may delay orgasm. Dopamine agonists, including anti-Parkinson's medications, can facilitate sexual receptivity and erection (see Figure 14.1). However, these responses appear to be dose dependent, related to how long medication has been used, and may differ for males and females (Clayton, 2007; Meston & Frohlich, 2000).

Dopamine	
Medications increasing available dopamine—tend to increase libido, arousal/erection, contradictory effects orgasm/ejaculation	**Medications decreasing or blocking dopamine**—tend to decrease libido, impair arousal/erection, delayed orgasm
bupropion	haloperidol, other typical antipsychotics
cocaine	clozapine, other atypical antipsychotics
bromocriptine	metoclopramide
levadopa	
ropinirole	
Serotonin	
Medications increasing serotonin—tend to decrease libido, arousal/erection; delay orgasm/ejaculation	**Medications decreasing or blocking serotonin**—tend to increase libido, arousal/erection, and shorten time to orgasm/ejaculation
fluoxetine and other SSRI's	buspirone
duloxetine, venlafaxine (SNRI's)	cyproheptadine
mirtazapine (agonist effects on postsynaptic 5-HT1A receptor)	mirtazapine (blocks 5-HT2 and 5-HT3 receptors)
Norepinephrine	
Medications increasing norepinephrine—tend to increase libido, arousal/erection, shorten time to orgasm	**Medications decreasing or blocking norepinephrine**—tend to decrease libido, arousal/erection; delay time to orgasm/ejaculation
bupropion	clonidine
mirtazapine	prazosin
duloxetine, venlafexaine (SNRI's)	propranolol
amphetamines	

SSRI=selective serotonin reuptake inhibitor SNRI=serotonin norepinephrine reuptake inhibitor

* Most psychotropic medications have activity involving more than one neurotransmitter, including others not listed here

Figure 14.1 Neurotransmitters and medication examples.*

Serotonin. Serotonin (or 5-hydroxytryptamine [5-HT]) signaling involves multiple receptors, and individuals may be at risk for developing depression from a composite of biological factors associated with components of 5-HT transmission (Jans, Riedel, Markus, & Blokland, 2006). Serotonin receptors appear to vary in their sexual effects: 5-HT1A receptors tend to facilitate libido, erection, and lower threshold for ejaculation, while 5-HT2 receptors appear inhibitory (Meston & Frohlich, 2000; Michael & O'Keane, 2000). Serotonin may also act in regulating neurovascular sexual response in the genito-urinary tract as well as centrally (Meston & Frohlich, 2000). SSRIs increase serotonin transmission, thus resulting in an overall inhibitory effect on sexual libido, arousal, and orgasm. Conversely, cyproheptadine antagonizes 5-HT2 receptors and seems to reverse SSRI-induced sexual effects (Moll & Brown, 2011; see Figure 14.1).

Norepinephrine. Deregulation of norepinephrine transmission, rather than a straightforward decrease in the level of activity, appears to play a significant role in depression (Delgado & Moreno, 2000). Centrally, norepinephrine facilitates sexual arousal and orgasm, while, peripherally, norepinephrine maintains vasoconstriction and inhibits erection (Clayton & Montejo, 2006). Antidepressants with relatively high noradrenergic effects, such as bupropion and duloxetine (Table 14.1), tend to have fewer sexual side effects than serotonergic agents.

The neuropathophysiology of depression and sexual dysfunction, though complex and not well understood, share common mechanisms. Because of these complex interactions, sexual difficulties may act as a life stressor preceding a mood disturbance, may present as a symptom of depression, or may develop as a side effect of antidepressant treatment.

Antidepressant Medications and Sexual Function

For patients and their care providers, depression often presents a treatment dilemma in terms of sexual function. As noted above, MDD appears to impact multiple areas of sexual function in both men and women, particularly in terms of desire and arousal. Many antidepressant medications, however, are associated with sexual side effects, resulting in decreased adherence to therapy (Ashton, Jamerson, Weinstein, & Wagoner, 2005; Nurnberg et al., 2008). A 2009 meta-analysis of the rate of treatment-emergent sexual dysfunction among the major antidepressants showed rates from 25.8% to 80.3%, with the highest rates among serotonergic

Table 14.1 Prevalence of Sexual Dysfunction among Common Antidepressants

	Desire Dysfunction (% patients)	Arousal Dysfunction (% patients)	Orgasm Dysfunction (% patients)	Total Sexual Dysfunction (% patients)
Citalopram	77.9	73.5	50.5	78.6
Sertraline	61.8	53.8	51.8	80.3
Fluoxetine	64.5	53.5	46.1	70.6
Paroxetine	67.9	62.0	57.1	71.5
Venlafaxine	61.1	66.6	48.2	79.8
Duloxetine	17.6	17.6	N/A	41.6
Mirtazapine	20.4	14.3	22.4	24.5
Bupropion	3.9	6.4	8.9	10.4
Imipramine	24.1	26.3	27.2	44.4
Placebo	3.8	3.5	6.7	14.2

Reprinted with permission from Serretti, A., & Chiesa, A. (2009). Treatment-emergent sexual dysfunction related to antidepressants: A meta-analysis. *Journal of Clinical Psychopharmacology, 29*(3), 259–266.

drugs: citalopram, fluoxetine, paroxetine, sertraline, and venlafaxine (Serretti & Chiesa, 2009). However, the rates varied significantly depending on the specific drug and type of sexual impairment (see Table 14.1). Of note, bupropion and mirtazapine demonstrated low rates of sexual side effects compared to placebos (Serretti & Chiesa, 2009). The rate of antidepressant-induced sexual dysfunction can vary according to the method used to assess sexual function, with direct verbal inquiry absent any questionnaire underestimating the incidence. In addition, inadequate treatment of depression rather than antidepressant use may play a larger role in sexual dysfunction, particularly those involving low desire. In a recent study of women with HSDD and depression, antidepressants users with inadequately treated depression had increased severity of HSDD and reduced sexual desire compared with women in remission. Antidepressants use itself was not associated with sexual function differences among women with HSDD and diagnosed depression (Clayton et al., 2012).

Sexual dysfunction induced by serotonergic antidepressant medications can be treated by a variety of techniques: watchful waiting, dose adjustment, drug holidays, switching medications, and adjunctive medication (Clayton & Montejo, 2006). If patients are not greatly distressed by the sexual side effects, about 30% of patients will experience moderate to total improvement in sexual function after six months (Serretti & Chiesa, 2009). Alternatively, the dose of medication may be reduced altogether or held for a day or so before sexual activity. The latter approach is effective only with medications with a short half-life time, such as paroxetine or sertraline, and requires planning sexual life (Zemishlany & Weizman, 2008).

If clinically appropriate, switching to an alternative medication with less risk of sexual dysfunction should be considered, such as bupropion (dopaminergic; Clayton, McGarvey, Abouesh, & Pinkerton, 2001; Thase et al., 2005) or mirtazapine (antagonistic activity at the 5-HT2 receptor; Gelenberg et al., 2000). Bupropion has also been shown to be effective when used as an antidote to SSRI-induced sexual dysfunction (Moll & Brown, 2011; Safarinejad, 2010; Safarinejad, 2011). Sildenafil, a selective phosphodiesterase type-5 inhibitor, has shown benefit in reversing SSRI-induced arousal/erectile and orgasm sexual dysfunction in both men and women (Nurnberg, Hensley, & Lauriello, 2000; Nurnberg et al., 2008; Rudkin, Taylor, & Hawton, 2004). Other adjunct medications with mixed evidence for efficacy include amantadine, bromocriptine, cyproheptadine, and buspirone (Moll & Brown, 2011).

Evaluation of Sexual Dysfunction

Sexual health is experienced through physical, intellectual, emotional, interpersonal, and spiritual domains, involving interaction among thoughts, body, and the outside world (Robinson, Bockting, Rosser, Miner, & Coleman, 2002; Robinson,

Feldman, Striepe, Raymond, & Mize, 2003). Sexual function thus depends on a complex congruence of biological (e.g. medications, systemic disease), psychological (e.g. self-esteem, body image), and sociocultural factors (e.g. education, religion), including life cycle events (Althof et al., 2005). Evaluation and treatment of sexual dysfunction should begin with a core assessment of the sexual issues and these potential biopsychosocial factors (Lindau, Laumann, Levinson, & Waite, 2003). The clinician's history should define the nature of the problem specifically in terms of libido, arousal, orgasm, or pain, as well as establish the time of onset within the context of life events, relationships, and sexual development.

Validated Instruments for Evaluating Sexual Dysfunction

Self-report instruments may be used to identify individuals with sexual functioning difficulties, and responses can guide further inquiry into problem areas. A variety of instruments have been developed to measure sexual function, and some of these instruments have been used with individuals who are also experiencing problems with depression (Rizvi, Yeung, & Kennedy, 2011). Two widely used measures are discussed here, one for use with women and the other for men. The Female Sexual Function Index (FSFI) (Rosen et al., 2000), is a 19-item, self-administered questionnaire. The measure comprises six domains—desire, subjective arousal, lubrication, orgasm, satisfaction, and pain—and women are asked to reflect on the past four weeks when responding to items. The FSFI has been used to discriminate between clinical and nonclinical populations. The developers of the FSFI recommend that the measure be used with women who have engaged in some sexual activity during the measurement period.

The International Index of Erectile Function (IIEF; Rosen et al., 1997) is a self-administered questionnaire that has been validated in 10 languages. The IIEF is a 15-item questionnaire assessing sexual functioning over the past four weeks and comprising five factors: erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction. IIEF erectile function factor scores can be used to determine severity of erectile problems: none, mild, moderate, and severe. The measure has been shown to detect treatment-related changes in men with ED, and the First International Consultation on Erectile Dysfunction recommended its use as a valid and reliable measure in clinical trials of treatment for ED (Rosen, Cappelleri, & Gendrano, 2002). The IIEF items focus on vaginal intercourse and for this reason this scale is only useful with heterosexual men. A five-item version of the IIEF was developed as a clinical screening measure for ED (Rosen, Cappelleri, Smith, Lipsky, & Pena, 1999.)

Psychosocial Assessment

In clinical settings, self-report instruments may be used as a tool in screening for sexual dysfunction, but these instruments should not be viewed as a substitute for a comprehensive diagnostic evaluation. To definitively diagnose a sexual disorder, an interview including a review of sexual, medical, and psychosocial history is required. The interview should also include assessment of the patient's experience of his or her sexual response (desire/interest, arousal, orgasm) as well as any pain symptoms. When difficulties in any of these aspects of sexual functioning are identified, further assessment guided by diagnostic criteria is required before any diagnosis can be made. Duration and frequency of symptoms should be ascertained. Importantly, men and women with significant symptoms of depression and sexual dysfunction may maintain frequency of sexual activity, thus frequency should not be considered in establishing sexual dysfunction diagnoses (Cyranowski et al., 2004; Howell et al., 1987).

Issues surrounding the diagnosis of HSDD are discussed at length because it provides the best example of challenges inherent in diagnosing sexual disorders in the context of depression. Symptoms of a depressive episode may include markedly diminished interest or pleasure in all, or almost all, activities (American Psychiatric Association, 1994), and for this reason lack of sexual interest and pleasure may be expected in individuals experiencing a depressive disorder. In fact, some estimates suggest as many as 70% of individuals with MDD also report low libido (Casper et al., 1985). It is important for the clinician who is conducting the assessment to recognize the potential overlap in criteria for diagnosing depressive and sexual disorders and to consider whether comorbidity is present. In the set of *DSM-IV* diagnostic criteria for HSDD, Criterion B stipulates that the sexual problem must cause marked distress or interpersonal difficulty and Criterion C directs the clinician only to diagnose a sexual disorder when another Axis I diagnosis (e.g., MDD) cannot better account for the presence of the sexual symptoms (American Psychiatric Association, 1994). In our example of HSDD, if deficient desire for sexual activity is merely a reflection of a general loss of interest and pleasure in all

or almost all activities and the individual does not report distress related to his or her sexual interest problems, a comorbid diagnosis of HSDD may not be indicated.

Timing of symptom onset may also assist the clinician in identifying if comorbidity is present. If the individual reports symptoms of sexual dysfunction prior to onset of depression, the diagnosis of sexual dysfunction in addition to MDD should usually be made. When onset of symptoms of depression and sexual dysfunction are coincident, it is incumbent on the clinician to determine whether the sexual dysfunction diagnosis should also be included; that is, whether the sexual symptoms are present to the extent that both sexual dysfunction and MDD diagnoses are warranted.

DSM-IV diagnostic criteria for diagnosing sexual dysfunctions related to arousal, orgasm, ejaculation, and pain focus largely on physiological and functional aspects of sexual response, and in this way criteria do not overlap with criteria for diagnosing a depressive episode. For these disorders, determining that the sexual dysfunction is not better accounted for by MDD should not provide the same challenges as the clinician may encounter with HSDD.

Medical Assessment

A thorough medical history should include acute and chronic medical problems, reproductive history, family history, lifestyle practices (tobacco, alcohol, substance use, diet, and exercise), and evaluation of potential systemic, local, and iatrogenic disorders. Sexual dysfunction may be the first sign of systemic illness in a patient with a family history of atherosclerosis, hypertension, diabetes, or neurological or rheumatologic disease. Medications can affect all aspects of sexual function, with antihypertensive, antidepressants, and hormonal agents among the most common offending agents (Basson & Weijmar Schultz, 2007).

A thorough physical exam is important in identifying medical factors in sexual dysfunction. In the absence of hormonal deficiency or chronic systemic disease, the exam is often normal. Persons with chronic systemic disease or known gynecological pathology and women who are older than 65 years or who have been without routine medical care are more likely to have significant findings. The type of sexual dysfunction, the health history, and any physical exam findings should guide the selection of laboratory testing. Lab tests are often normal, unless there is additional evidence for a systemic condition. An important role for the provider is to educate the patient regarding the sexual problem and any links to medical conditions. Patients need to be made aware that *correcting a biomedical condition will not necessarily restore sexual function* and that associated medical conditions are often contributing factors rather than the sole cause of sexual problems (Basson & Weijmar Schultz, 2007).

Treatment Approaches

As noted above, sexual dysfunctions are generally classified into disorders of desire, arousal, orgasm, or sexual pain, and depressed men and women are more likely to show impairments in sexual desire than other aspects of sexual function. Taken as a whole, however, men and women demonstrate significantly different patterns of sexual dysfunction, with varying associations to depression. Treatment approaches will vary depending on the type of sexual dysfunction, as well as the age, gender, and comorbid medical and psychiatric conditions for each patient. Even if depression is understood as a result of the individual's distress around his or her sexual difficulties, treatment should include a focus on depression. Patients may present with their own theory of the links between their sexual dysfunction and their mental health problems. For example, a patient with ED may conclude, "If it wasn't for my erection problems, I wouldn't have problems with depression." In these cases, it is important to provide education to the patient regarding the links between sexual dysfunction and mood: Even though his depression began after ED, the depression may continue to impact erectile function. However, a general psychological and medical treatment framework may be applied across most situations.

Psychological Interventions

Few studies of psychological interventions for MDD have included a focus on treatment for sexual dysfunction. These few studies have employed empirically supported treatments for treating depression, namely cognitive behavioral and interpersonal psychotherapies, and have included measures of sexual functioning. Another approach to treating comorbid difficulties with depression and sexual functioning is to provide interventions for individuals with sexual dysfunction and also measure changes in depressive symptoms. The studies focused on treating depression are discussed first followed by the sex therapy intervention studies.

A cognitive behavioral therapy (CBT) intervention study with German men and women diagnosed with an anxiety disorder and/or a depressive

disorder explored whether sexual dysfunction would improve as a by-product of a standard CBT intervention. These individuals completed measures of sexual functioning before and after CBT treatment, which averaged 30 sessions per individual. A description of how CBT was operationalized with these patients was not provided. Only results for the subgroup diagnosed with a moderate or severe depression (N = 49) and reporting symptoms of sexual dysfunction are discussed here. Within this subgroup, continued difficulty with symptoms of sexual dysfunction were reported by patients who experienced complete remission from depression (35.7%), those who had some positive response to therapy (47%), and those who had less than a moderate response to therapy for depression (83%; Hoyer, Uhmann, Rambow, & Jacobi, 2009). Specific aspects of sexual functioning were not reported for the depressed subgroup, thus it is unclear which aspects of sexual functioning may have improved and which aspects of functioning may have remained unchanged or worsened.

A small-scale CBT intervention study for men diagnosed with MDD included more specific details on various aspects of functioning and found some improvements in sexual functioning following the intervention. Importantly, these men were medication-free and thus results were not confounded by any effects of antidepressant medications on sexual function. Again, details of the CBT intervention were not described beyond duration and frequency: 20 50-minute sessions over 16 weeks. The men who experienced remission from depression also experienced significantly improved sexual satisfaction while the group of men who remained depressed did not. Sexual interest, drive, and fantasies did not significantly improve with remission from depression. However, within the entire sample, improvement in symptoms of depression was significantly associated with increased sex drive and decreased complaints about sexual functioning (Nofzinger et al., 1993).

A larger study providing a cognitive-behavioral intervention for men and women with MDD (N = 681) found improvement in some areas of sexual functioning posttreatment (Zajecka et al., 2002). Participants who were taking psychiatric medications completed a wash-out period, and all participants were randomly assigned to one of three treatment arms: nefazodone, cognitive behavioral analysis system of psychotherapy (CBASP), or combined treatment. Again, the psychological intervention provided (CBASP) was developed to treat depression, and no information was provided on any modifications targeting sexual functioning. Mean number of CBASP individual sessions for the two groups receiving psychotherapy was 16 sessions over the 12-week intervention.

A determination of sexual dysfunction was based on participants' dichotomous (yes/no) answers to questions regarding arousal, lubrication, orgasm, and ejaculation. Participants answering *yes* to any of these questions were classified as experiencing a sexual dysfunction. The percentage of women reporting sexual dysfunction significantly improved from baseline (48%) to end of intervention (35%) across all treatment groups. However, when looking at specific areas of sexual function for women (i.e., subjective arousal, lubrication, and orgasm) no significant improvements over time were found. No significant improvements in the percentage of men reporting sexual dysfunction were found following treatment (pretreatment = 65%, posttreatment = 58%). The effects of the intervention were also assessed in terms of participants' overall sexual interest/satisfaction score. Participants in the combined treatment group (psychotherapy and nefazodone) reported greater sexual interest/satisfaction than the psychotherapy-alone group; however, average rating for the combined group did not significantly differ from the average rating for the medication group.

The possibility that changes in depression levels may be associated with improvement in sexual functioning was also explored. Indeed, decrease in depressive symptoms was significantly related to increase in sexual interest/satisfaction ratings, and significant correlations were found across treatment groups over the course of treatment for both men and women. However, women's reports of sexual dysfunction (i.e., arousal, lubrication, orgasm) were not related to their level of depressive symptoms. In contrast, men's reports of sexual dysfunction (i.e., arousal and ejaculation/orgasm) decreased with lower severity of depressive symptoms. In sum, results of Zajecka and colleagues' (2002) intervention study were mixed, and the sexual functioning benefits of the interventions appear to be limited.

Interpersonal psychotherapy (IPT) is also an empirically supported treatment for depression, and one study explored potential benefits of this intervention on women's sexual functioning. Cyranowski and colleagues (2004) provided IPT for women ages 20 to 60 years old diagnosed with MDD and experiencing chronic difficulties with depression. Women who were taking

antidepressant medications prior to the study completed a washout period before entering the study. Study participants engaged in one-year of IPT (individual therapy), which included the provision of adjunctive SSRI treatment for women who did not respond to psychotherapy alone. As in the previously described CBASP intervention study, the IPT study also included self-report measures of sexual function at regular intervals. Of the 68 participants, 45 (66%) achieved remission from depression: 34 women achieved remission with IPT alone and SSRI treatment was added for 11 women to achieve remission. Among treatment remitters, significantly fewer women described the overall quality of their sexual functioning as inadequate. However, when considering specific aspects of women's sexual functioning (i.e., interest, arousal, orgasm), no significant changes were found with remission from depression. Associations between depressive symptoms and sexual functioning were explored after controlling for the effects of SSRI treatment and sexual-partner availability. Within the entire study sample, depressive symptoms were associated with negative global assessments of sexual functioning and decreased desire, sexual thoughts and fantasies, sexual arousal, and orgasmic function.

We identified only three studies providing treatment targeting sexual dysfunction and including a measure of depression, and all these studies focused on women. An 18-session individualized intervention developed for women with hypoactive sexual desire disorder, Orgasm Consistency Training, was provided to study women and their husbands (McVey, 1997). All women ($N = 131$) met *DSM-IV* diagnostic criteria for HSDD, and they were classified as nondepressed, mildly depressed, or depressed based on Beck Depression Inventory (BDI) scores. The depressed women had a higher attrition rate than the other two groups, and overall 59% of women did not complete Orgasm Consistency Training. BDI scores did not significantly change from pre- to posttreatment for any of the three groups. No significant relationship between depression severity and sexual functioning outcome measures were found. Improvement in sexual desire and motivation measures were found on some self-report measures but not others. Women collaborated with their therapists to develop individual treatment goals around their sexual functioning, and, regardless of their depression classification, women rated themselves as making significant progress toward these goals at conclusion of intervention.

A more recent study provided a mindfulness-based group psychoeducation intervention for women ($N = 26$) experiencing difficulties with sexual desire and/or sexual arousal. Of all studies discussed here, this study was the only one to deliver the intervention in a group format. Intervention components included education, CBT, mindfulness, sex therapy and relationship therapy. The primary goals of the intervention were to improve sexual desire and arousal; secondary goals included improving mood. Women engaged in three 90-minute group sessions. Prior to the intervention, the women's mean BDI score was consistent with mild depression, and changes in BDI scores posttreatment were not significant. However, measures of sexual functioning indicated significant improvement in desire and interest. Changes in measures of sexual arousal were mixed with little significant improvement found in validated self-report measures. Informal feedback provided by women identified mindfulness as the most helpful component of treatment; however, no formal analysis of treatment components was conducted (Brotto, Basson, & Luria, 2008).

One intervention study for women with vulvodynia, a subtype of dyspareunia, deserves mention here as it also included measures of depression. Women were randomized to 10 weeks of individual CBT or supportive therapy (SPT) sessions. CBT included specific education and practice around pain-relevant coping and self-management skills and included a focus on understanding sexual and emotional functioning, while SPT was nondirective and focused on assisting women in expressing their feelings. Attrition rate was 16% (no significant differences between groups) suggesting that the treatment was well tolerated. Women were asked to complete a measure of dyspareunia including frequency and intensity of pain during and after vaginal penetration as well as a measure of overall sexual functioning. For both groups, dyspareunia and overall sexual functioning self-ratings improved following the intervention. Dyspareunia ratings did not vary by treatment group; however, overall sexual functioning ratings improved more significantly for women in the CBT group versus the SPT group. Depression ratings improved for both groups, and no significant differences in improvements were found between groups. Overall, the CBT treatment appeared to provide some advantage over SPT, but SPT also provided benefits in terms of pain and mood improvements. Importantly, women in the CBT group reported greater treatment satisfaction and treatment credibility.

Methodological considerations including use of a variety of measures to assess sexual dysfunctions, and a variety of inclusion/exclusion criteria for study samples makes summarizing study results difficult. Most of the studies described here focused on treating depression and included measures of sexual functioning. The depression intervention studies did not identify a specific focus on treatment for sexual difficulties but merely measured sexual functioning outcomes as possible beneficial by-products of treatment for depression. Though some studies did find improvement in overall satisfaction or overall measures of sexual functioning with decreasing depression, findings were variable regarding specific improvements in sexual dysfunction in men and women, respectively. No depression intervention study reported significant improvement in both measures of overall and specific (i.e., desire/interest, arousal, orgasm) aspects of sexual functioning associated with treatment despite the relatively high number of treatment sessions (16–30) as well as the duration of treatment (i.e., up to one year). Rather, a consistent finding across these studies was the persistence of sexual functioning problems even with remission from depression.

Only three studies provided specific interventions targeting sexual dysfunction, and these studies focused on women only. With regard to depression ratings, the interventions for women with desire, interest, and/or arousal difficulties did not result in significant improvements. Following treatment, these women reported some improvement in sexual interest and arousal; however, findings were mixed with some measures showing no significant change in sexual functioning. The findings of the vulvodynia study were somewhat more encouraging as the interventions resulted in improvement in depression, pain ratings, and overall sexual functioning ratings across the two interventions, CBT and supportive therapy. These results do suggest; however, that the active intervention, CBT, had little benefit over the control intervention.

These studies leave us with some possible directions for future research. Because several empirically supported treatments for depression have been identified, the possibility that these treatments could also treat comorbid sexual dysfunction is appealing from an efficiency standpoint. Unfortunately, the findings described here do not allow us to draw this conclusion. Alternatively, the possibility that a sex-therapy intervention might result in improvement in comorbid depression provides another avenue for exploration. The success of a treatment may vary based on gender, specific sexual disorder, severity of depression, and the biopsychosocial profile of the patient (Althof et al., 2005). Future studies should include clinical assessment of participants such that individuals with comorbid diagnoses of MDD and specific sexual dysfunctions can be identified and efficacious interventions can be developed. Specific information on the components of study interventions (see Brotto et al., 2008, for example) must also be included so that findings can be replicated and successful interventions can be utilized by clinicians.

Although no specific psychotherapy treatment recommendations for comorbid depression and sexual dysfunction can be made based on the research described here, psychotherapeutic treatments for depression and sexual dysfunctions, respectively, have been developed (Heiman, 2002; Leiblum, 2007; LoFrisco, 2011; Riley & Segraves, 2006; Wincze, Bach, & Barlow, 2008). Treatments for male sexual dysfunctions have tended to focus on medications while pharmaceutical interventions for women have been less successful to date. Given this situation, it is likely that more emphasis will be placed on developing psychotherapeutic interventions as a primary modality for treating sexual dysfunction in women.

Medical Interventions

Medical interventions are most successful when individualized to the patient's history surrounding his or her sexual symptoms. Nonpharmacologic interventions include educating the patient regarding the multifactorial nature of sexual function, the normal sexual response cycles for men and women, and the general effects of aging on sexual response. Providers should assist patients in improving their overall health status, as better self-assessed health is correlated with less sexual dysfunction for both men and women (Lewis et al., 2010). Sexual dysfunction is associated with a number of systemic, chronic medical conditions including diabetes and cardiovascular disease. Identifying and optimally treating these conditions is critical to enhancing and preserving sexual function (Lue et al., 2004).

As noted previously, medications can contribute to sexual dysfunction through impact on neurotransmitters involved in sexual function, circulating hormone levels, or systemic effects of sedation or dryness. Discontinuing potentially offending medications where possible, along with alcohol and recreational drugs, is necessary, though often not sufficient, to resolve sexual issues. Depression

and anxiety should be adequately treated, while minimizing sexual side effects of medications. Underlying urologic and/or gynecologic conditions, such as lower urinary tract symptoms or vaginal atrophy, are associated with sexual dysfunction and should be addressed as well (Lue et al., 2004).

Pharmacologic interventions vary depending on the specific sexual disorder and any contributing factors. A comprehensive review of interventions is beyond the scope of this chapter; however, the most common medications and their uses are summarized in Figure 14.2 (Basson et al, 2004; Clayton & Hamilton, 2010; Lue et al., 2004). Of note, the evidence for bupropion's efficacy in treating female low desire, arousal, and orgasmic disorders is most notable in cases of SSRI-induced sexual dysfunction. Bupropion may also improve desire, arousal, and orgasmic functioning in nondepressed women, suggesting effects that are independent of mood (Safarinejad, 2010; Segraves et al., 2001; Segraves, Clayton, Croft, Wolf, & Warnock, 2004). The evidence for sildenafil's efficacy in treating impaired sexual arousal and orgasm in women is strongest in neurologically or SSRI-induced dysfunction, while testosterone-based interventions have the most evidence for improving desire and arousal in postmenopausal women (Basson, Wierman, van Lankveld, & Brotto, 2010; Clayton & Hamilton, 2010).

Female sexual pain disorders, such as vulvodynia (vulvar vestibulitis syndrome) are often treated with a variety of topical therapies including estrogen and topical anesthetics, as well as systemic pain modulators such as tricyclic antidepressants and gabapentin (Basson et al., 2004). Physical modalities are often used in these disorders as well, including pelvic floor physiotherapy and electromyographic biofeedback.

Conclusion

Depression and sexual dysfunction are both highly prevalent and commonly comorbid conditions, with profound bidirectional impact on each other. The medications used to treat depression may result in sexual side effects, yet controlling depression is critical to restoring energy, concentration, and the ability to experience pleasures that are critical to strong sexual function. A biopsychosocial approach to assessment and intervention, with a goal of maximizing overall health status, providing

Female Sexual Desire Disorder	Systemic ERT/HRT* (postmenopausal)	Bupropion*	Testosterone* (postmenopausal)
Female Sexual Arousal	Local (vulvovaginal) estrogen therapy (postmenopausal)	Bupropion* (especially SSRI induced dysfunction)	Oral Phosphodiesterase type 5 (PDE 5)Inhibitors* (strongest for SSRI-induced dysfunction)
Female Orgasmic	Local (vulvovaginal) estrogen therapy(postmenopausal)	Bupropion*	Oral Phosphodiesterase type 5 (PDE 5) Inhibitors* (strongest for SSRI-induced dysfunction)
Erectile Dysfunction	Oral Phosphodiesterase type 5 (PDE 5)Inhibitors	Intracavernosal Injection (ICI) Therapy: • Alprostadil (Prostaglandin E1) • Papaverine and combination+ Penthalamine	Inthraurethral alprostadil
Premature Ejaculation	Selective serotonin reuptake inhibitors (SSRIs)* Daily treatment – On demand treatment – Low daily doses + as needed higher dose 3-6 hours before intercourse.	Topical local anaesthetics (e.g., lidocaine)*	PDE-5 inhibitors (e.g., sildenafil).*
Male Ejacualtory, Orgasmic Disorders	Depends on etiology, no specific pharmacologic intervention		

* None of these drugs have received US Food and Drug Administration regulatory approval for this use

Figure 14.2 Pharmacologic interventions for common sexual dysfunctions.*

appropriate psychological therapies, and offering evidence-based medical interventions should yield the best outcomes.

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CHAPTER

15 Schizophrenia

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Abstract

Depressive symptoms commonly occur in individuals with schizophrenia-spectrum disorders. Empirical investigation of this comorbidity has revealed a number of interesting and potentially confusing findings. The purpose of this review is to summarize this literature, focusing on clinical, cognitive, behavioral, phenomenological, and neurobiological processes that are common and potentially disparate to these disorders. Additionally, the review will discuss four depression-related paradoxes that have emerged within the schizophrenia literature. It concludes with a brief summary of treatment considerations for patients with schizophrenia with comorbid depressive symptoms. It is hoped that this chapter can serve as an organizing framework for future research and can help focus efforts on designing new treatments for ameliorating depression-related symptoms in patients with schizophrenia.

Key Words: schizophrenia, depressive symptoms, comorbidity, depression-related paradoxes, cognition, treatment

Introduction

Schizophrenia is a severe mental disease associated with disruptions in a wide range of basic and higher-order cognitive, behavioral, affective, and interpersonal process. Although psychotic symptoms—such as delusions, hallucinations, and thought disorder—are generally considered the hallmark features of schizophrenia, affective symptoms, notably those involved in depression, have become increasingly important in clinical and empirical conceptualizations of the disorder. In this chapter, we provide a summary of historical, clinical, and epidemiological perspectives of depression in schizophrenia-spectrum disorders. In turn, symptomatological, neurocognitive, genetic, and neurobiological processes common to both schizophrenia and depressive disorders are discussed. We then focus on contemporary issues in schizophrenia-spectrum research, centering on four depression-related paradoxes and two potential psychological processes related to depressive symptoms in schizophrenia. The chapter concludes with a discussion of intervention and treatment issues.

In introducing the topic of comorbid depression and schizophrenia there are several important points to consider. First, there is an overwhelming amount of empirical research on this topic (e.g., more than 8,200 peer-reviewed entries using the keywords *depression* and *schizophrenia* in PsycINFO as of 1/1/2012). Accordingly it is impossible to meaningfully represent this entire literature in a single review. What we attempt to do, instead, is to provide a current summary of what is known about this topic as well as orient the reader toward what we believe to be the most compelling and theoretically interesting findings in the literature. Second, it is important to consider that the terms *depression* and *schizophrenia spectrum* are ambiguous. While diagnostic taxonomies such as the *Diagnostic and Statistical Manual of Mental Disorders Fourth*

Edition–Text Revision (DSM-IV-TR; American Psychiatric Association, APA, 2000) and the International Statistical Classification of Diseases and Related Health Problems (ICD-10) (World Health Organization, WHO, 1993) have helped to objectify these disorders for clinical purposes, lay people, researchers, and clinicians often use these terms quite differently. We conceptualize both depression and schizophrenia as potential end products of a cascade of genetic, epigenetic, learned, and other environmental influences. That is important to consider given that much of this review focuses on depressive symptoms and processes across the schizophrenia spectrum rather than the diagnostic overlap of the two clinical disorders. This perspective, that pathological symptoms and processes transcend traditional psychiatric nosology, is gaining traction in both clinical and research fields and is the conceptual thrust behind the current National Institute of Mental Health's Research Domain Criteria initiative (Insel et al., 2010) as well as potential revisions to the DSM-IV-TR. With that being said, we begin this review with a brief discussion of the historical significance of comorbid depression and schizophrenia.

Historical Perspectives

Early taxonomies of psychiatric disorders acknowledged that depression and psychosis often co-occurred. Emil Kraepelin's (1971) early diagnostic systems featured discrete disorders that, rather than being defined based on presenting symptoms, were based on time course and chronicity. It was acknowledged that symptoms such as those involved in depression and psychosis occurred across diagnostic categories. Particularly relevant to our discussion here is anhedonia—a cardinal symptom of both affective and psychotic disorders characterized by a reduced capacity to experience positive affect. In describing dementia praecox, a precursor to the term *schizophrenia*, Kraepelin (1971) noted that "profound damage occurs as a rule in the emotional life of our patients" (p. 32), which results in "the extinction of affection for relatives and friends" (p. 33) such that "even the fate of his nearest relatives affects the patient little or not at all. He receives visits without a greeting or other sign of emotion, does not enquire how they are, [and] takes no share in their joys or sorrows" (p. 33). Similarly, Eugen Bleuler (1950), a psychiatrist who coined the term *schizophrenia* in 1908, noted that in patients with schizophrenia "the fundamental affective symptoms often dominate the picture from the very start, in that the patients become increasingly indifferent and apathetic" (p. 254).

Early neurodevelopmental theories of schizophrenia also emphasized the importance of depression in schizophrenia-spectrum pathology. Sándor Radó (1962), who coined the term *schizotypy* to denote the personality organization suggestive of a liability for schizophrenia, conjectured that *anhedonia*, another term coined by Radó, was a critical component of schizotypy. As an extension of Radó's work, Paul Meehl (1962) proposed that anhedonia was a necessary component and cause of social isolation, social difficulties, and cognitive deviance in individuals with schizotypy (note revisions to this theory in Meehl, 1990, 2001). Both Radó (1962) and Meehl (1962, 2001) discussed the worsening of negative affective symptoms—dubbed *aversive drift*—such as guilt, grief, depression, shame, and anxiety over time in individuals with schizotypy. These symptoms, which dovetail with those seen in clinical depression, were considered universal in schizotypic individuals. Overall, the works of Kraepelin, Bleuler, Radó, and Meehl have by no means been lost to antiquity and, as seen throughout this review, serve as a framework for understanding schizophrenia-spectrum pathology.

Clinical Diagnoses, Epidemiology, and Comorbidity

Major Depressive Disorder

Despite historical emphasis on the overlap between depression and schizophrenia-spectrum disorders, there is surprisingly little overlap in the operational definitions of these two disorders. As detailed in ICD-10 (WHO, 1993) and DSM-IV-TR (APA, 2000), depressive episodes are defined with reference to distinct episodes of marked disturbances in mood functioning. The most common and, for the purposes of this review, important depressive disorder is major depressive disorder (MDD), which is marked by one or more depressive episodes. Major depressive episodes are identified on the basis of both (1) significant diminution of positive affect and (2) anhedonia, along with a set of somatic and physiological symptoms such as significant fluctuations in body weight and/or appetite, sleep and/or motor abnormalities, or cognitive symptoms including attention and concentration difficulties, suicidal ideation, and excessive feelings of worthlessness, guilt, and diminished self-confidence. In terms of clinical course, DSM-IV-TR and ICD-10 specify that the mood episode must persist for the majority of a

two-week interval while simultaneously resulting in social or occupational impairments to the individual. Apart from the symptoms and sequelae of mood disturbances per se, it is noteworthy that psychotic symptoms, such as delusions or hallucinations, are associated features of MDD and are thought to occur in approximately 5% of cases of major depression (Gaudiano, Dalrymple, & Zimmerman, 2009).

Schizophrenia

Schizophrenia is defined on the basis of symptoms of delusions, hallucinations, disorganized speech, markedly disorganized or catatonic behavior, and other negative symptoms. Negative symptoms are defined in terms of behavioral deficits that, as discussed below, conceptually overlap with symptoms of depression. Included among the negative symptoms are blunted affect (i.e., a reduction in postural, facial, and vocal-based affective expression), alogia (i.e., a reduction in the amount and rate of speech), and avolition (i.e., a reduction in motivated behavior). Importantly, anhedonia, which is widely considered a cardinal negative symptom (Blanchard & Cohen, 2006), is not included as a diagnostic criterion for schizophrenia for either DSM-IV-TR or ICD-10. Regarding the time scale of schizophrenia symptoms, DSM-IV-TR stipulates a relatively lengthy course, with at least two of the above symptoms being present during a one-month period with enduring signs of disturbance lasting at least six months and resulting in significant impairment in at least one domain of functioning.

The schizophrenia spectrum includes the "cluster A" personality disorders, notably paranoid, schizoid, and schizotypal personality disorders as well as schizophreniform disorder. The cluster A disorders are characterized by chronic schizophrenia-like traits that are generally less severe than those observed in schizophrenia but are present in late childhood or adolescence, are stable, and are of long duration; they affect multiple domains of functioning (APA, 2000). Schizophreniform disorder is characterized by symptoms that meet the criteria for schizophrenia but have not endured for at least six months. Most important for our purposes is to note that depression or even depressive symptoms (e.g., anhedonia) are not included as part of the diagnostic criteria for any of these disorders.

Schizoaffective Disorder

The term *schizoaffective psychosis* is credited to Jacob Kasanin (1933) and was originally used to describe individuals showing both psychotic and affective symptoms simultaneously. It was meant to capture patients whose illness was more episodic than that of those with schizophrenia; as such, it had a more favorable prognosis. Schizoaffective disorder was included as a subtype of schizophrenia in DSM-I and DSM-II and was recognized as a distinct disorder in DSM-III-R. Within DSM-IV-TR, schizoaffective disorder is operationalized in terms of meeting the criteria for a mood disorder, either major depression or manic episode, concurrently during an uninterrupted period of active schizophrenia symptoms. In addition, a period of active psychosis for at least two weeks in the absence of prominent mood symptoms for a "substantial" portion of the total symptom duration is required. Ambiguity involving the term *substantial* has been identified as an issue because it (1) obscures the diagnostic boundaries between schizoaffective disorder and MDD with psychotic features and (2) is insufficient for clarifying when schizoaffective disorder versus separate diagnoses of schizophrenia and mood disorder should be used (Lake & Hurwitz, 2006). To address this issue, there is ongoing discussion about modifying the criterion to require that the mood episode be present for a fixed amount of time. At the time of writing this review, the proposed criteria by the DSM-5 task force was more than half of the total duration of the illness (American Psychiatric Association, 2011).

Whether schizoaffective disorder is a meaningful addition to DSM-IV-TR and ICD-10 is a hotly debated issue. On one hand, numerous studies demonstrate the generally poor diagnostic stability of schizoaffective disorder (e.g., Schwartz et al., 2000), which, at the very least, points to the fact that existing diagnostic criteria do not provide clinicians with a firm foundation upon which to formulate prognostic and treatment judgments. Moreover, interrater reliability has been poor for schizoaffective disorder (Cheniaux et al., 2008), which is notable, given that interrater reliability for schizophrenia more generally has historically been good (Skre, Onstad, Torgersen, & Kringlen, 1991). On the other hand, schizoaffective disorder has been included in the DSM since its inception and is a common diagnosis employed in clinical practice. Thus there is a strong effort from the clinical community to retain schizoaffective disorder in the next iteration of the DSM. Summarizing this controversy at the American Psychiatric Association in 2009, William T. Carpenter noted that "[w]e had hoped to get rid of schizoaffective [disorder] as a

diagnostic category because we don't think it's valid and we don't think it's reliable. On the other hand, we think it's absolutely indispensable to clinical practice" (Carpenter, 2009). In accordance with its popularity in clinical settings, the current indication is that schizoaffective disorder will be retained in DSM-5.

With regard to conceptualizing the particular admixture of psychotic and mood symptoms that the label of *schizoaffective disorder* is intended to represent, at least four different conceptualizations have been put forth to explain the co-occurrence of these symptoms (Malhi, Green, Fagiolini, Peselow, & Kumari, 2008). First, with the least empirical support, it has been suggested that schizophrenia, schizoaffective disorder, and the mood disorders all represent discrete disorders with independent etiological, pathophysiological, and psychopathological properties (see Lake & Hurtwitz, 2006). Second, it has been proposed that schizoaffective disorder may be the reification of a statistical artifact in that the nosological entity is derived from the summation of symptom ratings and clinical reports for individuals with "genuine" schizophrenia with transient mood symptoms and individuals with a "genuine" mood disorder with transient or reactionary schizophrenic symptoms (e.g., see Kempf, Hussain, & Potash, 2005). Third, perhaps as a more parsimonious variant of the second model, schizoaffective disorder may reflect a subset of patients with a "genuine" schizophrenia or mood disorder with comorbid mood or schizophrenic symptomatology, respectively, and in which it is both clinically impossible and meaningless to adjudicate which set of symptoms is superimposed on the other. Finally, schizoaffective disorder may reflect the center region of a psychosis–mood disorder continuum anchored by "absolute" schizophrenia and affective disorder poles (Kempf, Hussain, & Potash, 2005; Lake & Hurwitz, 2006). Although not without appreciable shortcomings, evidence from fields as diverse as neuroimaging, genetics, neurobiology, epidemiology, and the cognitive sciences is beginning to accumulate in favor of the latter model. However, further work is needed in order to approach a greater consensus as to the interrelationship between severe psychotic and mood disturbances.

Clinical Epidemiology and Comorbidity

Several well-designed investigations have posited the average incidence of schizophrenia at 15 cases per 100,000 individuals, with lifetime prevalence of 0.7% (Tandon, Keshavan, & Nasrallah, 2008b; cf. Perälä et al., 2007). The epidemiology of other schizophrenia-spectrum disorders is somewhat less known; however, available estimates suggest that paranoid (e.g., 2% to 4%; Grant et al., 2004), schizoid (less than 1%; Weissman, 1993), and schizotypal (e.g., 3% to 4%; Johnson, Cohen, Kasen, Skodol, & Oldham, 2008) personality disorders have an equal or greater lifetime prevalence as compared with schizophrenia. The lifetime prevalence of schizoaffective disorder is currently unknown but is thought to be smaller than that associated with schizophrenia (APA, 2000). Given that many of the schizophrenia-spectrum disorders co-occur, particularly in the case of the cluster A disorders, it is unlikely that the lifetime prevalence rates for schizophrenia-spectrum disorders exceeds 5% of the population. Consistent with this figure, neurodevelopmental theories of schizophrenia have proposed that approximately 10% of the population has schizotypy, defined as the personality organization indicative of schizophrenia vulnerability, but that only a subset of these individuals will develop diagnosable schizophrenia-spectrum disorders (Meehl, 1962).

Lifetime prevalence estimates of clinical depressive disorders are much higher than those for schizophrenia-spectrum disorders. For example, data from the National Comorbidity Study, one of the largest epidemiological studies conducted in the United States to date, suggest that MDD occurs with a lifetime prevalence rate of approximately 15% (Kessler & Walters, 1998). Given that depression is a common occurrence in the population, one would expect that, by chance alone, almost one in five patients with schizophrenia-spectrum disorders would meet criteria for MDD at some point during their lives. The actual rates of clinical depression in patients with schizophrenia-spectrum disorders far exceed this estimate. For example, among individuals meeting criteria for schizophrenia, approximately 65% will also meet criteria for lifetime depression (Martin, Cloninger, Guze, & Clayton, 1985). It is also important to note that depression is consistently found throughout the course of schizophrenic illness. That is, depressive symptoms are elevated in patients during the premorbid (Addington, van Mastrigt, & Addington, 2003), prodromal (Lencz, Smith, Auther, Correll, & Cornblatt, 2004), first episode (Addington et al., 2003), and chronic phases of the illness (Harrow, Yonan, Sands, & Marengo, 1994). Depressive symptoms are also found in individuals with schizotypy identified via self-report questionnaire (Lewandowski et al., 2006)

suggesting that risk for depression and schizophrenia may be shared in some regard.

Shared Processes in Schizophrenia and Depression

Symptomatology

Despite the fact that there are no shared diagnostic criteria across depressive and schizophrenia-spectrum disorders (excluding schizoaffective disorder), there are many similarities in presenting symptoms across both disorders. A challenge in this regard is that different terms are often employed to refer to similar processes. Within schizophrenia, negative symptoms—which refer to deficits in affective, behavioral, and interpersonal processes—conceptually dovetail with many of the features associated with melancholic depression in that these features are also defined, in part, in terms of reductions in affective, behavioral, and interpersonal activities (APA, 2000). For example, as previously discussed, anhedonia, involving a diminished experience of positive affect, is a diagnostic criterion of major depressive episodes; it is a critical though not diagnostic feature of schizophrenia. Similarly, motivated behavior is affected in both disorders. Major depression is characterized by psychomotor retardation, defined in terms of visible slowing of movements and speech (APA, 2000)—a symptom set that resembles blunted affect and alogia in schizophrenia. Fatigue and loss of energy are both diagnostic criteria of major depression and are conceptually similar to the symptom of anergia seen in schizophrenia, characterized by lethargy and a lack of physical activity. Interestingly, studies comparing patients with schizophrenia and major depression in terms of the severity of these overlapping symptoms have generally found few group differences. For example, comparisons of patients in interview-based symptom rating scales of blunted affect, alogia, and anergia have found that they are comparable in severity (Tremeau et al., 2005). Similarly, a recent investigation employing acoustic analysis of natural speech to measure alogia and blunted affect found few group differences between patients with major depression and those with schizophrenia (Cohen, Najolia, Kim, & Dinzeo, 2012). Moreover, laboratory studies comparing patients with schizophrenia and depression on hedonic report following emotionally evocative stimuli have failed to find any group differences (Cohen, Callaway, Najolia, Larsen, & Strauss, 2012; Berenbaum & Oltmanns, 1992), suggesting that the severity of "in-the-moment" anhedonia is similar across these patient groups. In sum, a large body of research serves to indicate that there is considerable overlap in some diagnostic features of MDD and the negative symptoms of schizophrenia.

Beyond affective and behavioral deficits, neurocognitive deficits are also shared across the two disorders. A diagnostic criterion of major depressive episode involves a diminished ability to concentrate as well as indecision. Support for the validity of this symptom is found in a modest literature documenting small to medium effect-size deficits in individuals with depression compared with healthy controls on a wide range of neurocognitive abilities (Fleming, Blasey, & Schatzberg, 2004). While not a diagnostic criterion of schizophrenia, deficits in basic neurocognitive abilities, such as those involving attention and executive functions, is also well established in schizophrenia, though these deficits tend to be in the medium to large effect-size range compared with controls (Heinrichs & Zakzanis, 1998). Moreover, neurocognitive deficits in schizophrenia reflect one of the strongest predictors of social and occupational functioning compared with other disease features (Green, 1996). A handful of studies to date have compared neurocognitive profiles between depression and schizophrenia patient groups. Generally these findings suggest that patients with psychotic depression are similar in neurocognitive performance compared with schizophrenic patients, but that patients with nonpsychotic depression perform better than either patients with schizophrenia or those with psychotic depression (e.g., Jeste et al., 1996). In sum, neurocognitive impairments appear to be a feature of both MDD and schizophrenia and, to a large extent, reflect psychosis as opposed to any independent feature of either disorder.

Genetic Factors

Contributing to the explanation of the comorbidity between depression and schizophrenia mentioned above, there is an expansive literature (e.g., Huang et al., 2010) citing evidence of overlapping genetic factors to the respective depressive and schizophrenic phenotypes. For example, both family and twin studies have consistently reported that the risk of schizophrenia-spectrum disorders is elevated among relatives of those with mood disorders and, conversely, the risk of mood disorders is significantly elevated among relatives of those with schizophrenia (e.g., Aukes et al., 2012). In addition, evidence from twin studies, examining both monozygotic and dizygotic twin pairs, indicates that nonpsychotic co-twins in pairs discordant

for schizophrenia nevertheless have increased risk of mood disorders (Argyropoulos et al., 2008). Moreover, genetic linkage and association studies also provide support for overlap between these disorders. As yet, this collective body of research indicates that there is no universally agreed upon set of gene variants that appears necessary or sufficient to "cause" either schizophrenia or MDD. Instead, the consensus pictures of schizophrenia and MDD are that both cases represent complex, polygenic conditions with multiple underlying polymorphisms, each of which contributes small yet incremental etiologic effects (Gejman, Sanders, & Duan, 2010). Despite present uncertainty regarding the exact nature of shared and unshared genetic underpinnings, a review of this literature implicates several chromosomal regions, including 10p13, 13q32, 18p, and 22q11-q13 (Wildenauer, Schwab, Maier, & Detera-Wadleigh, 1999) and specific genes such as DISC1, COMT (catechol-*O*-methyl-transferase), and DRD1–4 (dopamine receptors D1-D4) in the etiology of both general psychosis (Levinson, 2003) and MDD (Levinson, 2005). In sum, it is noteworthy that there is at present a significant body of evidence indicating that there are at least some common genetic origins of both classes of psychiatric disturbance.

Neuropathology

Developments in an array of methodologies—such as structural and functional magnetic resonance imaging, spectroscopy, positron emission tomography, various electroencephalographic techniques, and single photon emission computed tomography—have enabled the isolation of several neurobiological features common to individuals with schizophrenia and those with MDD. From a purely structural or neuroanatomical perspective, overall reductions in brain volumes have been documented in schizophrenia (Steen, Mull, McClure, Hamer, & Lieberman, 2006) and, to a lesser extent, MDD (Soares & Mann, 1997), with specific reductions in hippocampal gray matter occurring in both conditions (Bremner et al., 2000; Steen et al., 2006). As reviewed by both Krystal, D'Souza, Sanacora, Goddard, and Charney (2001) and Winograd-Gurvich, Fitzgerald, Georgiou-Karistianis, Bradshaw, and White (2006), there are several of other neuroanatomical pathologies, housed in regions of the temporal and prefrontal lobes, that are common to schizophrenia and MDD; space considerations preclude us from detailing these here. However, one key point to note in considering all neuroanatomical abnormalities is that none reaches the level of diagnostic markers for either schizophrenia or MDD at this time, as the morphological changes are generally of small effect size and occur with varying degrees of frequency across a number of other psychiatric conditions (Steen et al., 2006).

In addition to structural pathologies, certain neurophysiological and neurochemical abnormalities have been found common to both schizophrenia and depression. For example, dysfunctions in non-REM sleep architecture and truncated REM sleep latencies have been found in both schizophrenia and affective disorders (Monti & Monti, 2005). Hypercortisolemia and dysfunctions in the hypothalamic-pituitary-adrenal axis are also implicated in both the onset and maintenance of major depressive episodes as well as being considered one of, if not the, physiological mechanisms mediating the onset of initial psychotic episodes as well as positive symptom exacerbations over the course of illness (Norman & Malla, 1993). Additionally, a more contemporary version of the "dopamine hypothesis" (Abi-Dargham, 2004) posits attenuated levels of cortical dopamine as underlying the anergia of schizophrenia; this last is easily conflated with the psychomotor retardation characteristic of MDD (i.e., a depressive symptom that is, likewise, putatively underpinned by hypodopaminergic activity) (Malhi, Parker, & Greenwood, 2005). In fact, fueled by indirect evidence from efficacy and effectiveness studies of several classes of drugs including the antidepressants and antipsychotics (Möller, 2003; Winograd-Gurvich et al., 2006), there is thriving interest in the other monoaminergic systems and their common inputs to schizophrenia and depression. At present, evidently, there are numerous convergences in the neurobiology of schizophrenia and depression; future research is likely to uncover further neuropathological overlaps.

Four Depression-Related Paradoxes Within Schizophrenia

Throughout the last six decades of research on depression-related processes in schizophrenia, some key inconsistencies in the literature have emerged. While this no doubt reflects, at least in small part, the sheer magnitude of this literature as well as increasing sophistication of methodological and theoretical tools available, four key paradoxes—the expression-experience paradox, the state-trait paradox, the schizotypy-schizophrenia experience paradox, and the deficit-depression paradox—have

emerged that are highly replicable across studies. In this next section, we briefly review these paradoxes and discuss what they might mean for our broader understanding of schizophrenia and major depression.

Paradox 1: The Expression-Experience Paradox

The first paradox involves a dysjunction between expression and experience in patients with schizophrenia. Flat affect or emotional blunting represents one of the core negative symptoms of schizophrenia and consists of impoverished verbal and behavioral emotional expressions ranging from generalized reductions in affective reactivity to the complete absence of emotional expression. Flat affect was at one point naturally assumed to signal reductions in the emotional and phenomenological experience of patients (Kraepelin, 1971). More recent evidence suggests, however, a paradox, in that patients' observable behavior belies their subjective experience, which is in some cases seemingly without discernible pathology (e.g., Horan, Kring, & Blanchard, 2006) and in others characterized by amplified rather than attenuated affective states (e.g., Horan et al., 2005). Several investigations have sought to explicitly document this paradox of dampened external emotional expression with normal or at least active emotional experience and, importantly, have done so using samples of neuroleptic- and otherwise psychotropic-naïve patients, which helps to disentangle psychopharmacologic artifact (i.e., akinesia masquerading as flat affect) from veridical negative symptomatology. For example, Kring, Kerr, Smith, and Neale (1993) presented a group of patients and nonpatient controls with a series of evocative film clips and recorded the participants' behavior during the clips. Immediately following stimulus presentations, participants were prompted to report on their emotional states using a standardized scale. Following conclusion of the study, participant videotapes were reviewed and coded for emotional expressivity. The results revealed that patients with schizophrenia were indeed less facially expressive than their nonpatient counterparts when viewing the evocative film clips; however, the patient group was also similar to the nonpatient group with regard to self-reported emotional experience.

As yet it is unclear what causes the expression-experience paradox. One potential explanation, the neuromotor dysfunction model, posits that expressive deficits are largely motoric in nature (see Dworkin, Clark, Amador, & Gorman, 1996). However, before concluding that schizophrenia patients, by virtue of their flat affect, are altogether devoid of a capacity for emotional expression, it is important to note some potentially contradictory findings. First, a handful of studies (e.g., Earnst et al., 1996) find evidence that patients nonetheless enact microexpressions, although usually below the threshold of unaided human perception and thus not qualifying as expressive behavior per se—that is, subtle, unobservable muscle twitches that serve as precursors to perceptible facial expressions. Thus patients on some level are expressing themselves behaviorally. Second, an examination of posed facial and vocal expressions in patients with schizophrenia suggested that flat affect was pronounced only for the expression of surprise and sadness but not disgust, happiness, fear, or anger (Putnam & Kring, 2007). These findings suggest that patients are, at least with some emotional states, able to express themselves in a normal manner when properly motivated. The authors of that study suggest that schizophrenia may be associated with higher thresholds for producing observable expression. As yet, however, the nature of this first paradox is unknown.

Paradox 2: The Trait-State Paradox

The second paradox concerns the nature of anhedonia in schizophrenia. As previously noted, anhedonia, defined as the inability to experience pleasant emotions, has long been considered a fundamental negative symptom of schizophrenia (e.g., Meehl, 1962). Support for this notion is found from studies employing self-report trait questionnaires of positive affect, where patients consistently report severely diminished range and frequency of pleasurable emotional experiences and also from studies where anhedonia is rated by trained clinical interviewers (e.g., Horan et al., 2006). In contrast to these findings, when patients report their "in the moment" pleasant experience—for example, in reaction to controlled laboratory stimuli within experimental paradigms or real-world events using experience sampling methodology—individuals with schizophrenia do not qualitatively differ from those without schizophrenia (see Cohen & Minor, 2010; Kring & Moran, 2008). In brief, across many studies employing numerous stimuli and designs, a hedonic experience paradox emerges whereby individuals with schizophrenia exhibit traitlike but not statelike anhedonia.

Five explanations for this incongruity in schizophrenic patients' trait and state pleasure

have been proposed, including the (1) anticipatory hedonic deficit, (2) affect regulation deficit, (3) encoding-retrieval deficit, (4) representational deficit, and (5) social-stimuli specific deficit hypotheses (Cohen, Najolia, Brown, & Minor, 2011). First, the anticipatory hedonic deficit hypothesis (Gard, Kring, Gard, Horan, & Green, 2007) posits that schizophrenia patients possess a relatively specific defect in "anticipatory" affective and cognitive neurocircuitry, which compromises their ability to accurately forecast pleasurable emotional experiences. In contrast, to the extent that the neural structures underlying the "consummatory" or online processing of affective stimuli are thought to be largely intact, schizophrenia patients in-the-moment experiences of pleasant emotions are comparatively normal. Second, the hypothesis suggesting deficits in affect regulation postulates that schizophrenic patients possess a specific deficit in implementing emotion-regulating strategies whereby they are unable to mitigate unpleasant emotional states; therefore disinhibited negative affect serves to contaminate pleasant emotional experience. In support of this hypothesis, a recent meta-analysis of 26 laboratory mood-induction studies in which pleasant and unpleasant emotional responses were measured separately using valence-specific rating scales found that, although schizophrenic patients did not generally report abnormal levels of in-the-moment pleasant emotion, they concurrently reported elevated unpleasant emotions across a broad range of stimuli (Cohen & Minor, 2010). In other words, patients with schizophrenia do not exhibit statelike anhedonia (i.e., diminished pleasant affective states) per se but instead experience pathological emotional experience in the form of disinhibited negative affect.

The third model of trait and state incongruity, the encoding-retrieval deficit hypothesis, suggests that in-the-moment affective experience is not disordered in schizophrenia but that, instead, there is a defect in encoding and/or recall of pleasant experience, which leads to unstable memory representations of these experiences or errors in the reconstructive memory process (Herbener, Rosen, Khine, & Sweeney, 2007). Not unrelated to this third model, the representational deficit hypothesis places explicit emphasis on the formation and utilization of memory representations. That is, the representational deficit hypothesis states that that traitlike but not statelike anhedonia in schizophrenia is thought to be the by-product of impaired associative learning whereby patients fail to pair valence (e.g., pleasant) with stimuli (e.g., hobby), which in turn undermines the pairing of stimulus and response (e.g., pleasure) (Gold, Waltz, Prentice, Morris, & Heerey, 2008). Last, the hypothesis suggesting a social stimuli–specific deficit postulates that individuals with schizophrenia possess a specific defect in experiencing pleasant emotion (i.e., anhedonia) in reaction to strictly social or interpersonal stimuli that manifests uniformly across trait and state contexts and that the apparent trait-state anhedonia inconsistency in schizophrenia is an artifact of the fact that previous studies of state emotional experience emphasized nonsocial stimuli (Blanchard, Horan, & Brown, 2001).

Paradox 3: The Schizotypy-Schizophrenia Experience Paradox

The third paradox concerns a disparity in anhedonia across the schizophrenia spectrum. As noted above, evidence that state anhedonia is present in schizophrenia has generally not been found in laboratory mood-induction studies (Cohen & Minor, 2010). Interestingly, state anhedonia has been reported in laboratory studies of schizotypy. Compared with control groups, individuals with schizotypy report less positive affect in response to laboratory stimuli. This is striking for two reasons: First, this finding is replicable across at least eight studies with, to our knowledge, only two null findings (for review see Cohen, Callaway, Najolia, Larsen, & Strauss, 2012). Second, the schizotypy groups were, without exception, recruited from college samples. The implication is that state anhedonia occurs in schizotypy but not schizophrenia, a notion paradoxical in that schizophrenia is by definition more severe in virtually every illness-related aspect compared with schizotypy, particularly in those recruited from a college setting. In a direct examination of this paradox, Cohen and colleagues (2012) compared two separate groups of schizophrenia patients: college students with psychometrically defined schizotypy and nonschizotypy college students in their subjective reactions to affectively valenced positive, negative, and neutral image stills as well as their trait report of positive emotion. With no exceptions, the schizotypy group reported significantly less positive affect for each of the three conditions than each of the other groups. Conversely, the schizophrenia group did not differ statistically from the control group for any of the conditions. Importantly, there were no differences in trait affect between the schizophrenia and schizotypy groups, suggesting that the seemingly

paradoxical group differences are limited to state anhedonia. These findings did not appear to reflect comorbid depression or anxiety.

Why would psychometrically defined schizotypal adults be more anhedonic than chronic outpatients with severe mental illness? At present, the answer to this question is not known. One possible explanation concerns the nature of self-reported emotion. Strauss and Gold (2012) have proposed an explanation using Robinson and Clore's (2002) accessibility model of emotional self-report. This model explicates the cognitive processes underlying emotional self-report under varying reporting conditions. State self-report is thought to recruit "online" systems, whereas trait self-report is thought to draw upon recall of episodic or semantic autobiographical belief systems. In this manner, state and trait response formats often elicit very different self-reports because individuals access different systems in completing them. Interpreted through this model, the state ratings can be taken as valid indication of patients' capacity to experience emotion "online," whereas persons with schizotypy cannot. Interestingly, in the Cohen et al. study (2012), both the schizotypy and schizophrenia groups displayed similar abnormal patterns of trait self-report, suggesting that they both share similar abnormally biased autobiographical beliefs regarding emotion. Thus clinical "anhedonia" may primarily reflect abnormal belief sets. For patients, this may be inconsistent with their true experiences, whereas for individuals with schizotypy, this matches their online experiences. It is also worth noting the possibility that individuals with schizotypy are better able to accurately incorporate their autobiographical beliefs, or to be "colored" by autobiographical biases, in reporting on-line. That is, owing to neurocognitive or other impairments, abnormal autobiographical beliefs may not affect patients' online reports the way it does for individuals with schizotypy. The accessibility model predicts that this would not be the case, as autobiographical memory is postulated to have little impact on online emotional reporting. Nonetheless, it is difficult to understand why college students with schizotypy would be more pathological than older, relatively chronic patients with schizophrenia; thus further research is needed in order to clarify this perplexing phenomenon.

Paradox 4: The Deficit-Depression Paradox

The fourth paradox involves a disparity in symptom severities within schizophrenia. In considering mental illnesses, it is important to acknowledge that there are no genetic, metabolic, anatomical, cognitive, or behavioral factors that are present in all, or often even most, diagnostic categories (Tandon, Nasrallah, & Keshavan, 2009). Thus it is important to consider heterogeneity within schizophrenia-spectrum and depressive disorders. With respect to the heterogeneity of schizophrenia symptoms, Carpenter and colleagues have proposed the "deficit syndrome" construct (Carpenter, Heinrichs, & Wagman, 1988). Patients with the deficit syndrome are those who meet the criteria for schizophrenia and also experience negative symptoms that are chronic (i.e., present for more than a year) and idiopathic (i.e., reflecting primary schizophrenia pathology as opposed to being secondary to medication side effects, paranoia, intellectual disability, or suspiciousness (Kirkpatrick, Buchanan, Ross, & Carpenter, 2001). Symptoms of the deficit syndrome include a range of negative symptoms such as restricted affect, poverty of speech, diminished emotional experience (e.g., anhedonia), diminished sense of purpose, diminished social drive, and curbing of interests. Collective evidence from nearly three decades suggests that approximately 25% to 30% of patients with schizophrenia suffer from the deficit syndrome and that these patients show poorer social, occupational (Strauss, Duke, Ross, & Allen, 2011), and neurocognitive (Cohen et al., 2007) functioning. Moreover, their negative symptoms tend to be strongly resistant to psychosocial and pharmacological treatments (Kirkpatrick et al., 2001). Interestingly not all sequelae associated with the deficit syndrome are prognostically negative. The deficit syndrome has also been associated with decreased use of illicit substances, lower rates of suicidality, lower rates of posttraumatic stress disorder, and less severe negative affect (Kirkpatrick, et al., 2001; Strauss et al., 2011). Of note, although deficit schizophrenic patients show abnormally high levels of anhedonia, they also show reduced overall depression on both interviewer-rated symptom measures and self-report scales (Kirkpatrick, 2001). Therein lies the paradox—that the schizophrenic patients with the most severe depressive symptoms—at least in terms of anhedonia, flat affect, psychomotor retardation, anergia, and attentional dysfunction—are also those with the least severe depression. As yet there is no clear resolution for this paradox, although it reflects an interesting conundrum for future research endeavors.

The Cognitive Underpinnings of Depression in Schizophrenia

With the increasing technological and methodological sophistication of techniques available to psychological scientists as well as the increasing collaboration by multidisciplinary teams, rather elaborate mechanistic accounts of depressive features in schizophrenia have been made possible. Many of these theories focus on the interplay between varying systems; for example, on the link between affective, cognitive, and behavioral components and processes. In the next section, we orient the reader to two of these emerging areas of research that attribute cognitive underpinnings to depressive symptoms in schizophrenia. These include a cognitive load theory of psychomotor retardation, blunt affect, and alogia as well as a higher-order cognitive theory for anhedonia.

Cognitive Load Theory: The Interplay Between Cognitive and Expressive Systems

In the nonpsychiatric population, affective expression is dynamic across contexts and is modulated by a number of factors. In particular, affective expression is influenced by an individual's affective experiential state and level of arousal (e.g., angry, happy) (Sobin & Alpert, 1999) as well as other environmental and contextual variables. Emerging evidence suggests that cognitive load may also reflect an important variable for understanding affective expression. In other words, cognitive resources, particularly those involved in attention and working memory, may be critical for effective expression (for a broader discussion of cognitive load theory see Plass, Moreno, & Brunken; 2010). Support for a link between cognitive load and expression is garnered from a recent study (Cohen, Dinzeo, Donovan, Brown, & Morrison, 2012) where speech from healthy adults during a dual-task condition designed to induce cognitive load (using a visual-based 1-back task) was compared with speech from a baseline condition without a cognitive load. Results suggested there was a significant decrease in speech production, inflection, emphasis (in women only), and intensity as a function of increased cognitive demands. These data suggest that there is a link between systems underlying cognitive resources (or at least in the systems related to the management of these resources) and those involved in vocal expression even in healthy adults.

Why might cognitive load be responsible for blunted affect and alogia in schizophrenia-spectrum disorders? First, cognitive deficits are well documented in individuals with schizophrenia (Heinrichs & Zakzanis, 1998), and cognitive deficits tend to be more pronounced in individuals with negative symptoms than patients without negative symptoms (Cohen et al., 2007). In our laboratory, we have found that the severity of attentional and working memory deficits, measured using standard neuropsychological tests, are significantly associated with increased average pause time, reduced number of utterances, and reduced emphasis measured during a laboratory speaking task in patients with schizophrenia (Cohen, Najolia, Kim, & Dinzeo, 2012). Collectively, these data suggest that those patients with the most limited cognitive resources are also those with the most severe expressive deficits. Second, emerging research employing dual-task methods in patients with schizophrenia have demonstrated that symptoms of alogia (defined in terms of reduced speech output) worsen in patients with schizophrenia when cognitive resources are taxed (e.g., Melinder & Barch, 2003). A recent study from our lab also provides evidence that cognitive load is related to expressive deficits in individuals with psychometrically defined schizotypy. Using a visually based working memory and simultaneous speaking task, we observed an interaction between cognitive performance and speech production and emphasis in schizotypal subjects versus controls. Increased errors on the working memory test were associated with reduced speech and emphasis significantly more in the schizotypy than the control group (Cohen, Morrison, Brown, & Minor, 2011).

A "cognitive resource" model is potentially important for understanding expressive deficits in schizophrenia for several reasons. First, if cognitive resources are important for understanding the severity of expressive deficits, this would suggest that assessment should occur under conditions where cognitive load can be controlled for or, preferably, be directly manipulated. Current assessment procedures typically measure expressive deficits during clinical interviews, where cognitive demands can vary dramatically. Second, a cognitive resource model may be helpful for understanding the cognitive and pathophysiological underpinnings of expressive deficits more generally. Of note, our model suggests the involvement of a resource bottleneck of some sort, potentially in the prefrontal cortex and dorsolateral anterior cingulate cortical structures, because these sites are implicated in working memory and deliberate cognitive effort (Kerns et al., 2004). Finally, potential interventions are indicated by this model. By relieving cognitive

load or improving cognitive resources more generally, it is possible that expressive deficits might be ameliorated in severity. In sum, clarification of the role of cognitive load in expressive deficits may yield important insights into the mechanism(s) underlying them and provide novel avenues for treatment.

"Higher Order" Cognitive Biases and Depression

Just as basic cognitive abilities may influence symptoms of depression in individuals with or without schizophrenia, higher-order cognitive abilities may play a key role. To introduce this topic, it is important to consider the role of higher-order cognitive biases in depression more generally. From a cognitive theory perspective (Beck, Rush, Shaw, & Emery, 1979), beliefs about oneself, one's environment, and one's future play a critical role in understanding one's affective states as well as their behavioral interactions with others and their environment. When these beliefs are overly pessimistic, they can lead to subjectively unpleasant mood states, loss of experience of pleasure, and a host of other symptoms associated with major depression (Beck et al., 1979; Gotlib, Krasnoperova, Yue, & Joormann, 2004). This model has been supported by over five decades of research into the role of cognitive biases in depression (e.g., Williamson, Muller, Reas, & Thaw, 1999). This is, in large part, the reason why this model serves as the basis for one of the most empirically efficacious and widely used psychosocial interventions to date—cognitive-behavioral therapy (CBT) (Butler, Chapman, Forman, & Beck, 2006). The question at hand concerns the link between higher-order cognitive biases and affective states in patients with schizophrenia.

The attribution of negative and depressive symptoms to higher-order cognitive biases in schizophrenia is particularly attractive for several reasons. First, it is well documented that schizophrenia is associated with a wide array of cognitive biases. For example, many schizophrenic patients show an increased threat-sensitivity bias for interpreting social interactions as being inaccurately hostile. This particular cognitive bias is thought to serve as a precursor to paranoid delusions (Penn, Ritchie, Francis, Combs, & Martin, 2002). Relatedly, patients show an array of attentional and autobiographical recall biases for selecting negatively valenced information (Waters, Badcock, & Maybery, 2006). Second, patients with schizophrenia suffer from a number of reality testing deficits (Blackwood, Howard, Bentall, & Murray, 2001), which serve to diminish their ability to accurately evaluate internal and external events once information has been processed. From this perspective, schizophrenic patients may not be able to accurately challenge biased cognitions that they experience. To date, depressive biases in schizophrenia have received only limited empirical attention. Grant and Beck (2009) examined group differences in self-reported defeatist beliefs between schizophrenic patients and nonpsychiatric controls and found that patients endorsed more severe defeatist beliefs at a large effect-size level. Within the schizophrenia group, the severity of defeatist beliefs was associated with more severe negative symptoms as well as poorer functioning, more impaired neurocognitive performance, and more severe depression overall. Similar results have been found in a separate study of ultra-high-risk patients—individuals with either a family history of psychosis combined with emergent functional decline or who are experiencing the presence of subthreshold psychotic symptoms (Perivoliotis, Morrison, Grant, French, & Beck, 2009). In this study, negative performance beliefs were associated with negative symptoms, suggesting that the link between cognitive biases and depressive/negative symptoms occurs in individuals before illness onset. In sum, emerging evidence suggests that biases in higher-order belief systems in patients with schizophrenia may explain basic interpersonal and affective phenomena related to major depression and often seen in patients with that disorder.

Implications for Treatment of Depressive Symptoms in Schizophrenia

Despite the clear importance of depressive symptoms in schizophrenia and the marshaling of significant research-related resources to understanding this link, there has been only modest success in treating depression in patients with schizophrenia. This reflects, in large part, the fact that most existing empirically supported treatments for schizophrenia have not been evaluated much in terms of their impact on depressive symptoms. Nonetheless, some published studies have focused on these symptoms in schizophrenic patients. In the following section, we focus on this burgeoning literature in terms of the pharmacological and psychosocial treatment of depression in persons with schizophrenia.

Pharmacotherapy

Psychopharmacology is typically considered a frontline treatment for both schizophrenia and major depression (Cardoni, 1997), and it is difficult

to dispute the dramatic effects that both first- and second-generation antipsychotic medications have on the psychotic symptoms associated with both disorders (Tandon et al., 2008b). The issue of treating depression in schizophrenia using pharmacotherapy is complicated, however. On one hand, there is much support for the notion that both first- and second-generation antipsychotics and a range of antidepressant medications can be useful in the treatment of depression and for "secondary" negative symptoms (reviewed in Singh, Singh, Nilamashab, & Chan, 2010). In addition, emerging evidence suggests that depressive symptoms in schizophrenia can be treated by antidepressants once patients are on a stable regimen of antipsychotic medication (Ivanets & Kinkul'kina, 2008). On the other hand, however, there is also evidence that the deficit symptoms of schizophrenia are unresponsive to antipsychotic interventions (Kirkpatrick, 2001). Moreover, there is limited consistency across studies in terms of which particular medications administered during which phases of illness and in which dosages are associated with the amelioration of depressive symptoms. Indeed, a recent review by Barnes and Paton (2011) advises that there is insufficient evidence at present to inform the clinical application of antidepressants for the treatment of negative and depressive symptoms and that therefore further research is needed to guide clinical practice. As a final note, in considering the pharmacologic treatment of depressive symptoms within schizophrenia, it is essential to recognize the dangers and complexities of mixing psychotropic medications. Polypharmacy and the use of augmenting agents are commonplace clinical practices; however, while some combinations of medications have the potential to improve prognoses, iatrogenic neurotoxicity is an ever-present risk; therefore these mixed treatment plans must be supervised closely and individually tailored in order to monitor the potentially dangerous side effects of psychotropic integration.

Psychosocial Interventions

At present, a variety of psychosocial treatments are considered to be empirically supported for the treatment of schizophrenia-spectrum disorders. While few of these treatments are designed to directly target symptoms of depression, several of these treatments have been evaluated for their success at ameliorating depressive symptoms. Social skills therapy is an example of one such intervention. Social skills therapy promotes social skill development through the use of role modeling, goal setting, and behavioral rehearsal and has been shown to foster the development of skills that patients utilize in the community and in everyday living (e.g., Bustillo, Lauriello, Horan, & Keith, 2001; Kurtz & Mueser, 2008.) A recent meta-analysis reviewed 22 randomized controlled trials (RCTs) that examined 1,521 outpatients with a diagnosis of schizophrenia or schizoaffective disorder in a variety of treatment settings. Overall this analysis found medium to large therapeutic effects (e.g., *d*'s = 0.40 to 1.20) in the acquisition of daily living and social skills as well as in their generalization to community functioning (Kurtz & Mueser, 2008). There are two reasons to suspect that social skills therapy may also ameliorate depressive symptoms. First, the aforementioned meta-analysis noted modest effects in the rehabilitation of negative symptoms (d = 0.40)—symptoms that are conceptually related to depressive symptoms. Second, an empirical study not included in the meta-analysis provides evidence that social skills therapy is directly associated with reductions in depressive symptoms—measured using clinical interview-based measures—as compared with "treatment as usual" (TAU) (Cui, Yang, & Weng, 2004). It is important to temper these findings with evidence that patients with deficit schizophrenia have been unresponsive to social skills therapy in at least one study (Kopelowicz, Liberman, Mintz, & Zarate, 1997), suggesting that depressive symptoms but not core negative symptoms, are responsive to social skills therapy. In sum, these data suggest that social skills training is an incrementally valid and at least modestly effective therapy for the treatment of certain negative and depressive symptoms of schizophrenia.

In addition to social skills training, CBT has been suggested as a treatment for schizophrenia-spectrum disorders (Bustillo et al., 2001; Tarrier, Haddock, Lewis, Drake, & Gregg, 2006; Wykes, Steel, Everitt, & Tarrier, 2008). CBT is a manualized therapeutic approach that includes skill development involved with identifying, questioning, and challenging automatic thoughts, goal setting, and emotional and cognitive awareness (Beck, 1997; Butler et al., 2006). Given that CBT has demonstrated appreciable short- and long-term successes as an intervention for depressive disorders (Butler et al., 2006), it is attractive as a potential treatment for depression in schizophrenia. Evidence for CBT's effectiveness in treating psychosis is generally favorable, although the magnitude of symptom amelioration is generally in the range of small to medium effect sizes. For example, a meta-analysis by Wykes and colleagues

(2008) revealed small improvements in effect size (*d*'s = 0.33 to 0.44) in patients' positive and negative symptoms as well as everyday functioning skills following specified treatment periods, although other analyses have reported more favorable findings (e.g., Tarrier & Wykes, 2004). A study by Tarrier and colleagues (2006) suggests that psychotic symptom improvement is not particularly durable, as remission in these symptoms for patients with schizophrenia treated with CBT disappeared at two-year follow-up. Moreover, with respect to changes in specific depressive symptoms, this study found no significant changes in suicidal ideation for those with schizophrenia treated with CBT. The Wykes et al. (2008) meta-analysis found that mood ratings significantly improved following CBT treatment programs, although some aspects of depression (i.e., feelings of hopelessness) remained unchanged. Taken together, the existing literature offers support for the efficacy of CBT for treating the myriad symptoms of psychotic illnesses. However, the typical magnitude of change and the durability of these changes is somewhat in question.

Finally, it is worth discussing the potential effects of cognitive remediation on depressive symptoms in people with schizophrenia. *Cognitive remediation* refers to a set of treatments meant to improve basic and social cognitive processes (e.g., Wykes, Huddy, Cellard, McGurk, & Czobor, 2011). The rationale of this treatment approach as applied to schizophrenia is that schizophrenia is associated with a wide array of neurocognitive deficits, typically on the order of one to two standard deviations (Heinrichs & Zakzannis, 1998), and that these deficits collectively reflect one of the most profound predictors of social and occupational functioning (Green, 1996). Thus improving patients' cognitive abilities might lead to meaningful improvements in general functioning. This is widely considered an efficacious treatment; however, its effectiveness is, at least in terms of real-world functioning, typically reported to be in the range of small effect sizes (Wykes, et al., 2011). There is reason to think that cognitive remediation, at least in theory, could help bolster basic cognitive abilities involved in affective regulation (e.g., cognitive control) such that symptoms of anhedonia and rumination are ameliorated. As yet, only a handful of studies have investigated the effects of cognitive remediation on depression in schizophrenia, and the evidence for its efficacy is mixed. On the one hand, Bark et al. (2003) reported that, in a study of 10 sessions of cognitive remediation therapy versus TAU in 54 patients with schizophrenia, there was a significant reduction in observer-rated depressive symptoms at four weeks following the cognitive remediation treatment. No significant reduction was observed for the control group. On the other hand, Lindenmayer and colleagues (2008) reported no significant change in depression from baseline to follow-up in a sample of 85 patients with severe mental illness randomized to 10 weeks of cognitive remediation or TAU. Moreover, Penades et al. (2006) compared the effects of a four-month-long treatment involving cognitive remediation versus CBT in 40 patients with chronic schizophrenia and reported that there was no significant change from baseline to six-month follow-up for the cognitive remediation group. Interestingly, the cognitive behavioral group showed a significant reduction in depression across the study period. As with the other psychosocial treatments discussed in this section, conclusions regarding the efficacy and effectiveness of cognitive remediation for depression in schizophrenia are tentative and dependent on future research.

Psychosocial Treatment of Schizoaffective Disorder

An alternate approach to understanding treatment for depression in schizophrenia is to review the literature on schizoaffective disorder, as many or most individuals meeting the criteria for this diagnosis have pronounced depressive psychopathology. While there is a sizable literature established on this topic, attempts to derive meaningful conclusions from it are complicated by several factors. First, many studies conflate manic and depressive symptoms (e.g., nonspecific "mood" symptoms); thus it is often difficult to tease apart treatment recommendations for symptoms of bipolar versus unipolar depression within the context of schizoaffective disorder. Second, there are at present no psychosocial treatments we could identify that have been developed specifically for schizoaffective disorder. Attention to this dearth of treatments has been suggested as a topic for future research (Jäger, Becker, Weinmann, & Frasch, 2010). Third, it is unclear in what respects potential treatments should differ from extant interventions for mood disorders and psychosis. Broadly speaking, illness characteristics such as psychosis severity, levels of functioning, severity of cognitive dysfunction, and treatment response are similar between patients with schizophrenia and schizoaffective disorders when demographic variables are controlled for (e.g., Bora, Yucel, & Pantelis, 2009; Irani, Seligman, Kamath,

Kohler, & Gur, 2012; Ritsner, Arbitman, Lisker, & Ponizovsky, 2012). From a psychosocial treatment perspective, therefore, it may be argued that there is little reason to treat schizoaffective disorder differently from schizophrenia, and that few findings from the treatment of schizoaffective disorder literature confer incrementally valid insights into treating depression within the schizophrenia spectrum.

Issues in the Psychosocial Treatment of Depression in Persons with Schizophrenia

While the development of empirically supported treatments of depression in schizophrenia is clearly in its infancy, some important insights can be gleaned from the literature for use in guiding the development of future interventions. First, treatments found effective in nonpsychotic populations must probably be significantly modified in order to transfer to schizophrenia populations. A host of disease (e.g., cognitive deficits, anergia, avolition) characteristics may complicate treatment compliance and should therefore be factored into the treatment. For example, all of the psychosocial treatments noted herein were designed for working with a population with profound cognitive deficits using clear, structured exercises and brief, easily comprehensible language. For this reason, therapies that have garnered substantial empirical support for the treatment of depression in nonpsychotic populations—which tend to be less structured, such as interpersonal therapy (IPT) (Markowitz & Weissman, 2012)—may need substantial modification to be appropriate for use with most schizophrenic patients. Second, schizophrenia is a dramatically heterogeneous disease; it will therefore be important to consider individual differences in terms of treatment response. For example, there may be cognitive, affective, symptomatic, or other characteristics that are critical predictors of treatment response (see Premkumar et al., 2011). As there are likely individual difference variables that predict psychosocial treatment response (e.g., deficit schizophrenia), it stands to reason to consider these symptoms in psychotherapy outcome research as well as in designing individually tailored treatment plans. Finally, it is important to approach treatment of depression in schizophrenia from a multidisciplinary perspective. A recent study by Grant, Huh, Perivoliotis, Stolar, and Beck (2012) highlights these last two points. The researchers combined pharmacological, community outreach, housing services, CBT, and other therapies to target negative symptoms of schizophrenia. In addition, the researchers tailored the CBT dependent on the patients' level of functioning and incorporated social skills training as well as insight recovery and remediation of attentional difficulties into each session. The results showed that participants who received the multidisciplinary treatment reported reduced avolition/apathy, improved global functioning, and motivational enhancement compared with the control group, who received only standard treatment. The authors discussed future therapeutic directions that individually tailor the needs of patients with schizophrenia, including adapting to functional capacity and neurocognitive deficits. They recommended that these changes be implemented so that outcomes regarding negative symptoms can be optimally targeted.

Summary and Conclusions

In summary, disease processes associated with both schizophrenia and depression are inextricably linked. The symptoms associated with these disorders often present similarly, and there appear to be convergences in the neurocognitive, neurobiological, and genetic processes underlying them. Despite this, a number of key inconsistencies and paradoxes have been revealed in the recent literature. We believe that the effort to understand these paradoxes reflects a critical endeavor for elucidating the nature of depressive symptoms and how they manifest in schizophrenia. A range of potential psychosocial and pharmacological treatment strategies for ameliorating depressive and negative symptoms exist for patients with schizophrenia, but none of them are uniformly supported by current evidence. Moreover, the benefits of many of these treatments appear to be modest at best. Future research, designed to clarify the mechanisms underlying these symptoms in schizophrenia, is important for designing new interventions. These directions may include modifying existing interventions that are empirically supported for nonpsychotic depression so that they will be appropriate for individuals with relatively severe interpersonal and neurocognitive dysfunctions. Further research on depression in schizophrenia will likely need to be multidisciplinary in nature so that it can effectively examine the involvement and interplay between behavioral, cognitive, and affective systems across a range of neurobiological systems. Additionally, RCTs that focus on psychosocial treatments that are tailored to individuals' functioning level and that encourage long-term or continuous treatment may be effective in targeting depressive symptoms specifically, in schizophrenia. Given the deleterious nature of these

symptoms and their impact to society at large, these are endeavors of prime importance.

Future Directions

1. Why do patients with schizophrenia report experiencing emotion "in the moment" but do not express emotion using hand gestures, facial expressions, or voice modulation?

2. Why do patients report that they do not experience much pleasure during clinical interviews and on trait questionnaires but report normal experiences "in the moment"?

3. To what degree would measuring reports of quality of life from individuals with schizophrenia-spectrum disorder help to determine depressive symptoms?

4. Why do individuals with psychometrically defined schizotypy, typically recruited from university settings, report experiencing "in the moment" anhedonia but patients with schizophrenia do not?

5. Why do patients with the deficit syndrome show a relatively high degree of certain depressive symptoms (e.g., psychomotor retardation, anhedonia), but low levels of clinical depression?

6. What is the link between cognitive resources and expressive deficits in schizophrenia?

7. What is the role of "higher-order" cognitive beliefs and biases in depression-related symptoms in schizophrenia?

8. To what degree do psychosocial and pharmacological interventions produce durable change in depressive symptoms for patients with schizophrenia?

9. To what degree are existing psychosocial treatments effective for ameliorating depressive symptoms in patients with schizophrenia?

10. What amendments can be made to psychosocial treatments to specifically target depressive symptoms of schizophrenia?

11. What individual difference characteristics are associated with treatment response for psychosocial treatments targeting depressive symptoms?

12. Should treatments be tailored to ameliorate symptoms of depression in schizoaffective disorder specifically, and if so, how would these treatments differ from CBT, cognitive remediation, and/or social skills?

13. To what degree does the treatment of negative symptoms relate to the treatment of depression in schizophrenia-spectrum disorders?

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CHAPTER

16 Suicide

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Abstract

Suicide is a significant concern for clinicians working with clients experiencing major depressive disorder (MDD). Previous research has indicated that MDD is the diagnosis more frequently associated with suicide, with approximately two-thirds of those who die by suicide suffering from depression at the time of death by suicide. This chapter reviews data regarding the prevalence of suicidal behavior among those with depressive disorders. It then reviews risk factors for suicide ideation, self-injury, and death by suicide. Finally, the chapter provides an empirical overview of treatment studies aimed at decreasing risk for suicide, as well as an overview of several recent treatment approaches showing promise in the reduction of suicidal behavior.

Key Words: suicide, major depressive disorder, suicide ideation, self-injury, death by suicide, depression, treatment approaches

Introduction

Suicide is a significant concern for clinicians working with clients experiencing major depressive disorder (MDD). The diagnostic criteria for major depressive episode include "recurrent thoughts of death (not fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide" (American Psychiatric Association, 2000). Previous research has indicated that MDD is the diagnosis most frequently associated with suicide, with approximately two-thirds of those who die by suicide suffering from depression at the time of death by suicide (Centers for Disease Control and Prevention, 2012). Estimates suggest that between 2% and 7% of adults with depression die by suicide (Bostwick & Pankratz, 2000; Inskip, Harris, & Barraclough, 1998). Bernal et al. (2007) indicate a population-attributable risk for suicide attempt of 28% among those with MDD. As such, it is critical that researchers and clinicians consider suicide risk in studies of depression and when evaluating or treating depression.

Prevalence

As noted above, suicide risk is a considerable concern in adults experiencing depression. One of the most recent investigations of the risk for suicide associated with different psychiatric diagnoses occurred within the National Comorbidity Study Replication (Nock, Hwang, Sampson, & Kessler, 2010). Nock and colleagues examined the odds ratio of several categories of thoughts or events related to suicide in a nationally representative household sample of 5,692 adults in the United States. Within this sample the odds ratio for lifetime suicide attempt was 5.1 for those with MDD and 4.9 for those with dysthymia. This suggests that adults with MDD are 5.1 times more likely to report a lifetime suicide attempt than those without MDD. Similarly, those with dysthymia were 4.9 times more likely to report a lifetime suicide attempt.

When other *Diagnostic and Statistical Manual of Mental Disorders* (fourth edition, text revision; American Psychiatric Association, 2000) disorders were controlled, these odds ratios decreased to 2.0 and .8, respectively; however, this does not diminish the clear impact of depressive symptoms (both alone and in combination with other disorders) on risk for suicide attempt. It is important to note that these odds ratios are among the highest of all Axis I disorders (i.e., among anxiety disorders, mood disorder, impulse control disorders, and substance use disorders). Further analyses indicated that mood and anxiety disorders contribute significantly to the onset of suicide ideation, whereas anxiety disorders alone contribute more to attempts among those with suicide ideation, with or without a plan for suicide (Nock et al., 2010).

Individuals experiencing more severe depressive symptoms or other comorbid diagnoses have higher rates of suicide. Studies have indicated that adults who have been hospitalized for depression (e.g., Conwell & Brent, 1995) and those who also experience a comorbid disorder (Cornelius et al., 1995; Oquendo et al., 2005) are at higher risk for suicide.

Previous research has also established gender differences in behaviors associated with suicide. It is well known that women attempt suicide more frequently, whereas the rate of death by suicide is much higher in males (Centers for Disease Control and Prevention, 2012). Oquendo et al. (2007) examined gender differences in predictors of suicide attempts or death by suicide in a sample of patients with *Diagnostic and Statistical Manual of Mental Disorders* (third edition, revised; American Psychiatric Association, 1987) MDD or bipolar disorder seeking treatment for depression. During the two-year study period, 16.6% of patients attempted or died by suicide. Significant predictors of these outcomes for men included family history of suicidal behavior, previous drug use, cigarette smoking, borderline personality disorder, and early parental separation. For women, previous suicide attempt, suicide ideation, lethality of previous attempts, hostility, subjective depressive symptoms, fewer reasons for living, borderline personality disorder, and cigarette smoking were all significantly associated with suicide attempt or death by suicide during this follow-up period. These data not only highlight gender differences associated with suicide behaviors but also elucidate the relation between gender, comorbid diagnoses, and increased risk for suicide behaviors.

Research has also examined differences in suicide rates and depression rates between ethnic groups. Oquendo et al. (2001) found that the one-year prevalence of MDD was highest for Caucasians (3.6%) followed by Mexican Americans (2.8%), Cuban Americans (2.5%), Puerto Ricans (.9%), and African Americans (.5%). The annual suicide rate in this study was higher for males than females, and authors found that Caucasian males had significantly higher rates of death by suicide than Mexican American and Puerto Rican males. Taken together, these data suggest the greatest risk for depression and death by suicide for Caucasian males. This may suggest cultural factors (e.g., social support, connectedness) that are protective against depression and suicide risk among other ethnic groups.

Risk Factors

As discussed above, approximately two-thirds of individuals who die by suicide suffer from depression at the time of their death (American Association of Suicidology, 2012); however, we know that many with depressive symptoms do not think about suicide or engage in self-injury behavior or suicide attempts. Given the extant empirical literature, there is evidence to suggest that the risk factors below are important for individuals with MDD. A recent review identified six of the most consistent risk factors for death by suicide: (a) social isolation, (b) prior suicide attempts, (c) mental health diagnosis (e.g., MDD), (d) family conflict, (e) physical illness, and (f) unemployment (Van Orden et al., 2010). Notably, these risk factors have been shown to influence suicide ideation, suicidal behaviors, and death by suicide.

Social Isolation

An examination of the literature indicates that social isolation (or variations of social isolation such as loneliness, social withdrawal, living alone, reporting few or no meaningful relationships, etc.) is a robust predictor of suicidal ideation, engaging in suicidal behaviors, and/or enacting a lethal or near lethal suicidal attempt (e.g., Baumeister & Leary, 1995; Conwell, Duberstein, & Caine, 2002; Heikkinen, Marttunen, Isometsa, & Lonnqvist, 1995; Van Orden et al., 2010). The literature indicates that lacking social relationships may lead to negative effects on psychological well-being, which in turn could lead to the manifestation of suicidal desire and/or eventual death by suicide (e.g., Baumeister & Leary, 1995; Shneidman, 1998; Van Orden et al., 2010). Baumeister and Leary (1995)

suggest that when a lack of belonging is apparent, severe deprivation ensues, which increases psychological distress and feelings associated with purposelessness. Social isolation has further been shown to predict suicidal ideation and behaviors across varying samples with differing demographics (e.g., age, ethnicity), medical conditions, and psychological problems (e.g., Baumeister & Leary, 1995; Compton, Thompson, Kaslow, 2005; Holt-Lunstad, Smith, & Layton, 2010; Mireault & De Man, 1996).

In considering the interactive effects of social isolation and depressive symptoms on suicidality, Au, Lau, and Lee (2009) found that the relation between depression and suicide ideation was weakened when individuals reported stronger family and peer relations. These data suggest that even when individuals report depressive symptoms, positive interpersonal relationships may decrease or buffer against suicide ideation. Conversely, research has shown that greater depressive symptoms and social isolation predict increases in subsequent suicidal behaviors and attempts (e.g., Holma et al., 2010).

History of Suicide Attempt(s)

Research indicates a history of suicide attempt(s) is one of the most robust and reliable predictors of death by suicide (Beautrais, 2002; Conwell et al., 2000; Gibb, Beautrais, & Fergusson, 2005). Suominen et al. (2004) conducted a 37-year follow-up study examining suicide risk after suicide attempt and found that 13 of the 98 participants had died by suicide. These results suggest that engaging in at least one prior suicide attempt is a potent risk factor for later death by suicide (Suominen et al., 2004). Literature further indicates that individuals who have engaged in repeated episodes of self-injurious behavior (Haw, Bergen, Casey, & Hawton, 2007), as well as those with a history of multiple suicide attempts (Joiner et al., 2009; Ortega & Karch, 2010; Zonda, 2006) are at higher risk for eventual death by suicide compared to those without a history of self-injurious behaviors. Interestingly, Holma et al. (2010) found that increases in suicide attempts were related to severity of depressive episodes, such that suicide attempts were highest for those reporting more enduring major depressive episodes (measured by duration of major depressive episode). These findings suggest that while a history of attempts is a robust predictor of subsequent suicidal behaviors, duration of major depressive episodes may be a key indicator of imminent suicidal crises (i.e., engaging in a suicide attempt).

Psychological Disorders

Literature indicates that those reporting psychological disorders are often at a higher risk for suicide ideation, suicidal behaviors, and death by suicide (e.g., Cavanagh, Carson, Sharpe, & Lawrie, 2003; Van Orden et al., 2010). In fact, Cavanagh et al. indicate that 90% of individuals who died by suicide had a diagnosable psychological disorder at the time of their death. It appears that the most prevalent psychological disorders for those who have engaged in either a nonlethal suicide attempt or fatal suicide attempt include mood disorders (e.g., MDD), personality disorders (e.g., borderline personality disorder), eating disorders (i.e., anorexia nervosa), schizophrenia, substance use disorders, and conduct disorder in adolescents (cf. Van Orden et al., 2010, for a more complete review).

Mood disorders, especially MDD, are the most common diagnoses for those who die by suicide (Moscicki, 2001;Van Orden et al., 2010). As noted above, Bostwick and Pankratz (2000) report that suicide rates for those diagnosed with MDD are between 2% and 6%. The literature also suggests that recurrent episodes of depression may be a more reliable indicator of eventual death by suicide than depression severity (Moscicki, 2001). There is a positive correlation between number of depressive episodes and suicide attempts (Ahrens, Beghofer, Wolf, & Muller-Oerlinghausen, 1995). Further, the potential for additional suicide attempts is higher for individuals with depression who have attempted suicide (van Praag & Plutchik, 1988). Nock et al. (2009) found that depression is a robust predictor of suicide ideation but fails to predict those planning a suicide attempt or those who have made a suicide attempt. In an additional study by Nock et al. (2010), posttraumatic stress disorder, conduct disorder, substance abuse disorders, and bipolar disorders were significantly associated with plans for suicide and suicide attempts. Taken together, these data suggest that depressive symptoms are more likely to predict suicide ideation (Nock et al. 2009), whereas disorders associated with deficits in impulse control and hyperarousal (posttraumatic stress disorder) are more likely to predict suicide plans and attempts (Nock et al., 2010). These findings highlight that depression, while increasing risk for suicide ideation, does not uniquely increase risk for attempting suicide (Nock et al., 2009, 2010).

Research examining other psychological disorders further indicates that borderline personality disorder (Duberstein & Witte, 2008) is associated with suicide deaths, such that 4% to 5%

of individuals with borderline personality disorder die by suicide (as cited in Van Orden et al., 2010). Those diagnosed with anorexia nervosa are 58 times more likely to engage in self-injurious behaviors and die by suicide compared to those without anorexia nervosa (Herzog et al., 2000). Suicide rates for those with schizophrenia range from 1.8% to 5.6% (Palmer, Pankratz, & Bostwick, 2005). Those diagnosed with a substance abuse disorder are 5.7 times more likely to die by suicide than the general population (Harris & Barraclough, 1997).

Family Conflict

Family conflict (e.g., familial stress, domestic violence, feeling one is a burden to one's family, household dysfunction) and a history of child abuse (e.g., physical and sexual abuse) are predictors of later suicidal behaviors for all ages (e.g., Bridge, Goldstein, & Brent, 2006; Duberstein et al., 2004). For example, Hetrick, Parker, Robinson, Hall, and Vance (2012) found that children and adolescents (n = 59) endorsing suicide-related behaviors (including attempting suicide and reporting suicide ideation) were more likely to have poorer family functioning even after accounting for depressive symptoms. Additionally, experiencing physical and sexual abuse as a child is a strong predictor of both lethal and nonlethal suicide attempts (Van Orden et al., 2010). Research further shows that exposure to familial suicide(s) and psychopathology (e.g., maternal depression) increases subsequent risk of youth suicidality (e.g., Randell, Wang, Herting, & Eggert, 2006). In a sample of potential high school dropouts, Randell et al. found that greater perceived family violence and stress (including familial alcohol and drug use) predicted those at higher risk for suicide. In addition, greater perceptions of familial depression were associated with increased risk for suicide. These data suggest that exposure to family dysfunction and psychopathology (e.g., familial depression) increase risk for youth suicide.

Physical Illness

Research on physical illness and suicide risk indicates that individuals reporting a medical illness are more likely to endorse suicide ideation and die by suicide compared to those without a medical illness (e.g., Conwell et al., 2010). In a study comparing the physical and psychological health of those who died by suicide (i.e., next of kin provided informant reports to ascertain a retrospective account of the victim's physical and psychological symptoms prior to dying by suicide) to a comparison group of community participants equivalent on demographic variables (e.g., age, gender), Conwell and colleagues found that older adults (i.e., 50 years and older) with greater physical illness (but not pain), functional impairment, and health-related needs had higher rates of death by suicide. A review by Robson, Scrutton, Wilkinson, and MacLeod (2010) indicated that individuals diagnosed with cancer die by suicide at higher rates than the general population (however, as noted, the prevalence of suicide ideation in cancer patients is comparable to the general population). Even so, Robson et al. reported that additional factors contributed to suicide deaths and suicide ideation in cancer patients, such as depression, hopelessness, type of cancer, impairment in physical functioning, and time since diagnosis with cancer. These additional factors are important to consider when evaluating physical illness and suicide risk as research indicates that not every physical illness (e.g., rheumatoid arthritis, diabetes, and hypertension; Harris & Barraclough, 1997; Stenager & Stenager, 1992) increases risk for suicidal behaviors. Importantly, a review conducted by Greydanus, Patel, and Pratt (2010) indicates that adolescents with chronic illness are at risk for suicide ideation and attempts, and depressive symptoms likely exacerbate risk for suicide. Greydanus et al. concluded that adolescents and young adults with chronic illness should be routinely assessed for depressive symptoms when evaluating suicide risk, as depressive symptoms likely increase the risk for suicidal actions.

Unemployment

Previous research also indicates that unemployment is associated with suicide ideation and death by suicide (e.g., Brown, Beck, Steer, & Grisham, 2000; Luo, Florence, Quispe-Agnoli, Ouyang, & Crosby, 2011; Waern, Rubenowitz, & Wilhelmson, 2003). For example, Luo and colleagues examined the relation between suicide rates (i.e., overall rate of suicide and age-specific rates of suicide) and business cycles in the United States during 1928–2007. Results reflected a general trend of suicide rates increasing during times of recession and decreasing during periods of economic improvement (Luo et al., 2011). More specifically, those ranging from 25 to 64 years of age were more likely to die by suicide during periods of recession but showed a decline in suicide deaths during economic expansions. In contrast, there was no association between suicide and economic climate for those younger than 24 or older than 65. This suggests that unemployment

may not be a direct predictor of suicide but rather may occur when other risk factors, such as increases in psychopathology (e.g., increases in depressive symptoms) or financial burden (cf. Luo et al., 2011) compound the negative effects of unemployment.

Additional Risk Factors for Death by Suicide

Other important indicators of risk for suicide include hopelessness, disturbances in sleep, agitation, combat exposure, homelessness, incarceration, access to lethal means, being exposed to suicide, and seasonal variations (cf. Van Orden et al., 2010). More research is needed, however, to better understand the role that these factors have on the development of suicide ideation and behaviors.

In light of findings regarding suicide risk, it is important to recognize that not everyone who has suicide risk factors will go on to experience suicide ideation or engage in suicidal behaviors. For example, literature indicates that depression increases risk for suicide ideation but does not increase risk of attempting suicide beyond its relation to suicide ideation (Nock et al., 2009). Verona, Sachs-Ericsson, and Joiner (2004) found that roughly 25% of depressed individuals reported a suicide attempt during their lifetime, and around 25% of the sample reported suicidal ideation within the previous two-week period. Therefore, while not everyone who has risk factors will go on to die by suicide, thorough assessment and monitoring of suicide risk is essential for these individuals.

Theories of the Development and Maintenance of Suicidal Behavior

Over the decades, research has produced many viable theories that help us to understand and predict suicidal behavior and eventual suicide deaths. Due to limited space, this chapter covers only the cognitive theory, the fluid vulnerability theory (FVT), and the interpersonal theory of suicide. The theories presented here are regarded as (arguably) the more prevalent, influential, and/or comprehensive theories related to suicide in recent decades.

Cognitive Theory

Beck's cognitive theory of psychopathology (e.g., Beck, 1967) is currently revered as one of the most influential theories for understanding depression, as well as understanding how maladaptive cognitive functioning contributes to suicide ideation and behaviors. A central tenet of Beck's cognitive theory suggests that faulty cognitions and/or misinterpreting events or experiences leads to psychopathology. This biased cognitive process inhibits adaptive functioning, leading people to engage in maladaptive cognitions and behaviors (Beck, 1967). Using Beck's cognitive theory of psychopathology as a theoretical foundation, Wenzel and Beck (2008) put forth a cognitive model for understanding suicidal behavior. As suggested, three primary constructs contribute to suicidal behavior: (a) dispositional vulnerability factors (e.g., trait characteristics such as deficits in problem-solving skills), (b) cognitive processes associated with psychiatric disturbances (e.g., maladaptive cognitions related to content information), and (c) cognitive processes associated with suicidal acts (e.g., engaging in thoughts or images of suicide; cf. Wenzel & Beck, 2008, for a comprehensive review).

Dispositional vulnerability factors are characterized as trait variables that increase the chances of experiencing psychiatric disturbances and engaging in suicidal acts, especially during times of stress. Wenzel and Beck (2008) propose five psychological dispositional vulnerability factors that are correlated with suicide ideation and/or behaviors: (a) impulsivity, (b) deficits in problem-solving skills, (c) over-general memory style, (d) trait-like maladaptive cognitive style, and (e) personality. These five factors are associated with suicidality as they likely generate initial distress that may activate psychiatric disturbances and suicidal crises (Wenzel & Beck, 2008). These trait factors mitigate or inhibit adaptive coping during suicidal crises (Wenzel & Beck, 2008). Thus individuals with more dispositional vulnerability factors are more likely to experience greater psychiatric disturbances and require less stress to activate cognitive processes associated with suicide (Wenzel & Beck, 2008).

These dispositional vulnerability factors are considered more distal factors related to general abnormal behavior or functioning, whereas cognitive processes associated with psychiatric disturbances and suicidal acts (i.e., the second and third constructs proposed) are more proximal constructs for understanding suicidal behavior (Wenzel & Beck, 2008). Cognitive processes associated with psychiatric disturbances are maladaptive cognitions related to content information (i.e., *what* people think about) as well as biases in information processing (i.e., *how* people think about information; cf. Wenzel & Beck, 2008). The cognitive model posits that during times of stress, cognitive processes are biased due to underlying schemas (i.e., schemas are internal structures that retain prior experiences

and cognitions so that new information can be readily interpreted and organized; Clark & Beck, 1999; Wenzel & Beck, 2008). These schemas result in processing information using negative cognitive content (as opposed to adaptive or positive cognitive content; Wenzel & Beck, 2008). Thus as the frequency, intensity, and duration of psychiatric disturbances (or negative and maladaptive cognitions) increase, the potential for engaging in the cognitive processes associated with suicidal acts also increase.

In particular, Wenzel and Beck (2008) indicate that the cognitive processes associated with suicidal acts are maladaptive cognitions related to specific suicidal content information and information processing (e.g., engaging in suicide ideation and/or behaviors, activation of the hopelessness schema). As distress becomes unbearable and can no longer be tolerated, individuals will engage in suicidal acts (Wenzel & Beck, 2008). As proposed, suicidal individuals utilize suicide schemas in times of stress. An example of a suicide schema is chronic or trait hopelessness. Research indicates that chronic hopelessness is a strong predictor of suicide deaths (Dahlsgaard, Beck, & Brown, 1998); therefore, the activation of the hopelessness schema is detrimental to adaptive functioning and promotes engagement in suicidal thoughts and behaviors (Wenzel & Beck, 2008). It is suggested that the desire to engage in suicide ideation and behaviors emerges from activation of suicide-relevant schemas, biased information processing of suicide-related cues (e.g., fixating on suicide as the only option), and increases in psychiatric disturbances during times of stress (Wenzel & Beck, 2008).

Taken together, the cognitive model of suicidal behavior proposes that these three constructs work in tandem during times of stress that lead individuals to desire suicide (Wenzel & Beck, 2008). Specifically, the greater number of dispositional vulnerability factors, along with increases in severity, duration, and frequency of cognitive processes associated with psychiatric disturbances and greater use of cognitive processes associated with suicidal acts, will increase the likelihood that an individual will act on his or her suicidal thoughts and potentially die by suicide (Wenzel & Beck, 2008). Empirical research generally supports a cognitive model of suicidal behavior. Briefly, numerous outcome studies have supported the efficacy of cognitively based therapies for reducing suicide ideation and suicidal behaviors (see Treatment section below; e.g., Brown et al., 2005). Results from such studies generally indicate that cognitive therapy techniques (e.g., exploring the cognitive triad and the suicidal mode and cognitive conceptualization of a recent suicide attempt) contribute to reductions in suicide ideation and intent (e.g., Brown, Jeglic, Henriques, & Beck, 2006).

Fluid Vulnerability Theory

Rudd (2006) expanded on Beck's cognitive theory by incorporating key principles of cognitive theory and applying them to suicidal individuals. The Fluid Vulnerability Theory (FVT; Rudd, 2006) helps to explain the process by which individuals experience acute and enduring suicide ideation and behaviors. The FVT proposes that triggering events (i.e., events that induce suicidal thoughts and behaviors), the duration of a suicidal state (i.e., how long someone will desire death by suicide), and the severity of ideation are fluid in nature (Rudd, 2006). Even though the FVT suggests that individuals differ on triggering events, maintaining factors, severity, and duration, it is argued that suicidal vulnerability for each individual is still measurable.

It is important to note that the FVT incorporates the principles of cognitive theory and the *mode* to understand suicidality (i.e., risk, behaviors, ideation, and activation). Expanding on the concept of the suicidal mode mentioned briefly in Beck (1996), Rudd (2006) hypothesized that the suicidal mode consists of four domains: (a) the cognitive system, (b) the affective system, (c) the behavioral or motivational system, and (d) the physiological system.

Within the FVT, the cognitive system of the suicidal mode incorporates suicidal thoughts, the cognitive triad (i.e., the individuals' view of themselves, the world, and the future; e.g., Beck, 1970), conditional assumptions (e.g., "by helping everyone in my family, they will love me"), and compensatory methods (e.g., perfectionism; cf. Rudd, 2006, for full review of the FVT). The affective system includes emotions such as loneliness, shame, and depression. Within the behavioral system of the suicidal mode, individuals engage in suicidal behaviors such as writing suicide notes, gathering materials to enact a suicide attempt, and attempting suicide. Last, the physiological system is activated through heightened states of arousal (Rudd, 2006).

There are eight assumptions of the FVT:

1. Individuals experiencing an active suicidal episode will not be able to sustain the episode indefinitely; rather active suicidal events are time limited.

2. The threshold (i.e., baseline) for which an individual will go from being *not* at risk for suicide to actively suicidal is uniquely variable for every individual (i.e., everyone has a different baseline risk).

3. After experiencing acute risk for suicide, individuals will return to baseline.

4. People with previous attempts have an increased baseline compared to those with no attempt history.

5. Aggravating factors (i.e., internalizing or externalizing stressors such as depression and poor interpersonal relationships) will increase risk for suicide.

6. The severity of aggravating factors (e.g., greater depressive symptoms) and baseline risk will predict the severity of suicidal events, such that those with a higher baseline risk (e.g., multiple attempters) and more severe aggravating factors will experience more severe suicidal episodes.

7. Aggravating factors will only increase risk of suicide for a limited amount of time.

8. If aggravating factors are targeted and treated effectively, acute risk will be mitigated and the individual will return to baseline (e.g., Rudd, 2006).

The theory argues that sufficiently identifying and remedying (or reducing) these eight factors will reduce suicide risk.

To date, little empirical research has been conducted to test the FVT. Bryan, Johnson, Rudd, and Joiner (2008) investigated characterological traits (e.g., borderline traits) that are likely to distinguish between suicidal groups (i.e., single attempters who will not make a subsequent attempt and single attempters who will go on to make an additional attempt) in active-duty military personnel reporting a sole past suicide attempt. Results generally failed to support the FVT theory. That is, personality traits did not distinguish between future multiple attempts and true single attempts. The results did suggest that hypomanic symptoms differentially predicted future multiple attempts when compared to true single attempts. Bryan et al. suggest that this finding provides partial support for the FVT, such that poor affect regulation (i.e., hypomanic symptoms) is reflective of elevated baseline risk and the potential for acute suicidal activation.

Interpersonal Theory of Suicide

In roughly the past decade, the interpersonal theory of suicide (cf. Joiner, 2005; Van Orden et al. 2010) has blossomed as one of the leading theories related to the etiology of suicide. The interpersonal theory of suicide posits that individuals are most likely to enact a lethal suicide attempt when they (a) feel a thwarted sense of belonging (i.e., thwarted belongingness), (b) perceive themselves to be a burden on others (i.e., perceived burdensomeness), and (c) have acquired the ability to engage in a lethal suicide attempt (i.e., acquired capability).

Thwarted belongingness occurs when an individual desires a sense of belonging or connection with others, but this need to belong is thwarted (Van Orden et al., 2010). It is comprised of two components: loneliness and nonreciprocal caring relationships (Van Orden et al., 2010). Experiencing both loneliness (e.g., having little to no social connections) as well as lacking caring reciprocal relationships will result in the greatest sense of thwarted belongingness (Van Orden et al., 2010).

Perceived burdensomeness occurs when individuals feel as though they are a burden to those in their life. Similar to thwarted belongingness, perceived burdensomeness is comprised of two components: feelings of self-hatred and feeling as though one is a liability to others (i.e., thinking that one's death is more beneficial than one's life). When an individual experiences both feelings of self-hatred and of liability, this will produce the greatest perceptions of burden (e.g., Van Orden et al., 2010).

It is further purposed that experiencing thwarted belongingness or perceived burdensomeness will lead to passive suicide ideation (i.e., a wish for death; Van Orden et al. 2010). Passive suicide ideation is contrasted with active suicidal ideation—a desire to engage in suicidal behaviors that results in a fatal suicide attempt (e.g., planning and preparing to take one's life). For passive suicide ideation to escalate to active suicidal desire (i.e., actively wanting to kill one's self), perceived burdensomeness and thwarted belongingness must co-occur in the presence of hopelessness. That is, when an individual believes that there is no hope that his or her perceived burden on others and thwarted sense of belonging will end, active suicidal desire will arise (Van Orden et al., 2010). However, the interpersonal theory of suicide posits that wishing for death (passively or actively) is not sufficient for engaging in a lethal suicide attempt. Rather, one needs the ability to enact a lethal suicide attempt (i.e., acquired capability; Van Orden et al., 2010).

According to the interpersonal theory of suicide, the capability to die by suicide (i.e., acquired capability) is also comprised of two components: reduced

fear of dying and an increased tolerance to physical pain (Van Orden et al., 2010). As one becomes less afraid to die and has the ability to tolerate more lethal forms of self-injury, the more likely someone will be to enact a lethal suicide attempt. The ability to engage in a lethal suicide attempt, however, is not simple or easy. Rather one needs to acquire this ability over time through repeated exposure to painful and fear-inducing experiences, which, in turn, leads to habituation and the activation of the opponent process (i.e., when an individual experiences two opposing valences, the most reinforcing valence will manifest into observable behaviors; cf. Solomon & Corbit, 1974; Van Orden et al., 2010). Once habituation to painful and fear-inducing events occurs, individuals may begin to engage in progressively more painful and lethal methods of self-injury (Van Orden et al., 2010). For example, the first time an individual engages in self-injury (e.g., cutting), this will likely create painful and/or fear-inducing responses. This initial response (i.e., increases in pain and/or fear), however, will stabilize overtime through repeated exposure to such events. Given that the initial stimulus (e.g., self-injury) no longer produces the same initial effects (due to habituation), the individual will have acquired the ability to engage in more painful and/or fear-inducing behaviors, thus beginning the progression toward more painful and lethal methods of self-injury. Therefore, the greatest risk for suicide is evident when someone has acquired the ability to produce a lethal suicide attempt as well as feels hopeless about changing feelings of thwarted belongingness and perceived burdensomeness (i.e., acquired capability; Van Orden et al., 2010).

To date, empirical research largely supports the tenets proposed in the interpersonal theory. Research indicates that perceptions of burdensomeness and thwarted belongingness predict suicide ideation in diverse samples, such as undergraduates, those reporting suicide attempt(s), methadone outpatients, and psychotherapy outpatients (cf. Ribeiro & Joiner, 2009, for full review). Research further supports acquired capability as a risk factor for suicide. Smith and colleagues (2010) indicated that suicide attempters were more insensitive and fearless to pain compared to suicide ideators and controls, consistent with the interpersonal theory's description of acquired capability. Joiner and colleagues (2009) tested the interpersonal theory in a clinical sample of young adults reporting severe suicidality (i.e., recent suicide attempt or imminent risk of suicide). Results showed that those with the highest perceived burdensomeness and thwarted belongingness and those with a suicide attempt history (i.e., used as a proxy for acquired capability) were significantly more likely to attempt suicide compared to those with less severe perceived burdensomeness, thwarted belongingness, and no attempt history. To date, few studies have examined the direct relation between depressive symptoms and constructs included in the interpersonal theory. Davidson, Wingate, Grant, Judah, and Mills (2011) recently examined the effects of anxious and depressive symptoms on the constructs proposed in the interpersonal theory. Findings indicated that after controlling for age, income, and gender, social anxiety predicted thwarted belongingness and greater depressive symptoms predicted both thwarted belongingness and perceived burdensomeness. These results suggest that depressed individuals may be at greater risk for developing perceived burdensomeness and thwarted belongingness, therefore increasing risk for suicide ideation (Davidson et al., 2011).

Assessment and Treatment

The above review of risk factors for death by suicide and theoretical ideas regarding originating and maintaining factors for suicidal behavior provide directions for assessment, as well as prevention and intervention approaches to reduce suicidal behavior. It is imperative that practitioners assess suicide risk in all patients so that appropriate steps can be taken for both safety management and treatment planning. We recommend the use of an approach that emphasizes risk and protective factors with empirical ties to suicide attempts and death by suicide.

Joiner, Walker, Rudd, and Jobes (1999) describe an empirically based approach to risk determination that focuses on previous attempt status, risk factors for suicide, and current desire and plans for suicide. This approach begins with the assessment of previous suicide attempts. Existing research has demonstrated that a history of multiple suicide attempts is associated with significantly greater risk than for a patient with no history of attempt or a single attempt (Joiner et al., 2005). Following the assessment of suicide attempt history, practitioners should assess current desire for suicide (i.e., suicide ideation, death ideation) and the presence of plans and preparations for suicide. Finally, practitioners should evaluate known risk factors for suicide, such as age, race, solitary living situation, unemployment, family conflict, physical illness, psychological disorder, and hopelessness.

There are two instruments we find particularly helpful in assessing these variables: the Modified Scale for Suicide Ideation (Miller, Norman, Bishop, & Down, 1986) and the Suicide Status Form–III (Jobes, 2006). The Modified Scale for Suicide Ideation is administered by the practitioner with scale items that have been associated with Suicidal Desire and Ideation and Resolved Plans and Preparation in a factor analytic study (Joiner, Rudd, & Rajab, 1997). The Suicide Status Form–III includes self-report and interview questions, providing information related to attempt history and current desire and plans for suicide, as well as risk factors for suicide. In their suicide risk decision tree, Joiner and colleagues (1999) suggest at least moderate risk for suicide for any patient with a history of multiple suicide attempts and any other significant risk factor. For patients without a history of multiple suicide attempts, practitioners should consider evidence of plans and preparations for suicide, considering risk moderate for patients with evidence of plans and preparations for suicide, as well as any other significant risk factor. Finally, for patients without a history of multiple attempts and little evidence of plans and preparations for suicide, risk is considered moderate for patients with evidence of suicidal desire and ideation, as well as two or more other significant risk factors. Practitioners are encouraged to review suggestions by Joiner and colleagues (1999) and Cukrowicz, Wingate, Driscoll, and Joiner (2004) for actions to ensure safety for patients at different levels of suicide risk.

A variety of psychosocial approaches to treatment are reviewed below. Despite the variety of approaches used to reduce suicidal behavior, the rate of suicide deaths has remained consistent in recent years. One reason for this, noted by Comtois and Linehan (2006), is dissemination. As these authors note, even when effective treatments are developed, approaches to dissemination often fall short, such that practitioners are not aware of these treatments or find the necessary elements, knowledge, or infrastructure required for delivery challenging.

Review of Efficacy Studies Associated with Reduction of Suicide Deaths or Self-Injury

Several comprehensive literature reviews have attempted to summarize the empirical literature on psychosocial treatment approaches for suicidal behavior. It is important to note that studies aimed at reducing suicidal behavior often include participants suffering from depression; however, many other psychiatric diagnoses may be present in participants. As such, the summary that follows is applicable to those with depression, but studies may have included patient populations based on different inclusion criteria (e.g., borderline personality disorder). Comtois and Linehan (2006) found only one randomized controlled trial that obtained a significant difference between a control condition and an experimental condition for deaths by suicide. Motto and Bostrom (2001) attempted to determine if ongoing long-term contact with individuals at risk for suicide would act as an effective suicide-prevention modality. Motto and Bostrom randomized patients who refused follow-up care or discontinued treatment prior to 30 days following hospitalization for depression or suicide risk. Patients were randomized to usual care or an experimental condition that included regular communication (24 contacts over 5 years) via a letter from a research staff member who had interviewed them. Significant differences were found for survival over the first two years, including a longer time to suicide death for participants in the experimental condition.

Comtois and Linehan (2006) also reviewed studies examining the efficacy of treatment approaches targeting self-inflicted injuries (i.e., deliberate self-harm, suicide attempts). Several approaches led to significant differences between experimental and control conditions. Studies that included a clinical management or outreach efforts led to significant differences when they included outreach following missed appointments (van Heeringen et al., 1995); in-person follow-up following admission for a suicide attempt (compared to telephone or no follow-up; Termansen & Bywater, 1975); and in-home monitoring that included psychotherapy, crisis intervention, and family therapy (Welu, 1977). Interestingly, similar studies including outreach efforts did not show benefit for self-inflicted injury (e.g., Cedereke, Monti, & Copenhagen, 2002; Chowdhury, Hicks, & Kreitman, 1973). Research indicates that outreach may be effective in some cases but does not benefit patients in other cases.

Among psychosocial treatment approaches, cognitive behavior therapy (CBT) has received the most attention. A variety of specific treatments have been developed, typically including elements such as the development of safety plans, problem-solving, distress tolerance, increasing hope and reasons for living, improving social resources, emotion regulation, and relapse prevention (e.g., Brown et al., 2005;

Linehan, Armstrong, Suarez, Allmon, & Heard, 1991; Rudd, Joiner, & Rajab, 2001; Salkovskis, Atha, & Storer, 1990). As noted by Comtois and Linehan (2006), outcome studies have indicated that CBT approaches have been effective in reducing suicide attempts or self-injury (Brown et al., 2005; Linehan et al., 1991; Salkovskis et al., 1990). These treatments range from a five-session, problem solving oriented CBT to the one-year treatment approach including weekly individual therapy plus group skills training. Among other psychosocial approaches that have been evaluated, interpersonal therapy (Guthrie et al., 2001) and a group therapy approach including elements of CBT, as well as psychodynamic therapy (Wood, Trainor, Rothwell, Moore, & Harrington, 2001) have resulted in reductions in self-injury or suicide attempts.

Interestingly, a number of trials evaluating CBT have also failed to impact future self-injury. Comtois and Linehan (2006) noted the primary elements of these treatments: a brief CBT self-help manual plus in-person sessions (Evans et al., 1999; Tyrer et al., 2003), problem-focused therapy (Gibbons, Butler, Urwin, & Gibbons, 1978; Hawton et al., 1981, 1987; van der Sande, van Rooijen, Buskens, & Allart, 1997), and a comparison of skills training to problem solving (McLeavey, Daly, Ludgate, & Murray, 1994) or to supportive therapy (Donaldson, Spirito, & Esposito-Smythers, 2005). It is unclear whether the limited support for these treatments is a result of less intensive therapy or differences in the content of these treatments as compared to those described above that were associated with reduction in self-injury or suicide attempt.

To provide the reader with a general overview of the components and structure of many cognitive or cognitive behavioral approaches to treatment of suicide risk, we review the 10-session cognitive therapy approach used by Brown and colleagues (2005). Brown et al. (2006) indicate that the early sessions of this treatment (typically sessions one through three) focus on engaging the client in treatment, orientation to the cognitive model (i.e., education about links between thoughts, feelings, and behaviors, as well as activation of the suicidal mode), developing a safety plan (i.e., steps the client should take when he or she experiences thoughts and feelings associated with suicide attempt), and creating a cognitive conceptualization of a recent suicide attempt. The middle phase of treatment (typically sessions four through seven) includes the active targeting of suicidal behavior. Together the therapist and client begin to identify maladaptive core beliefs that are common when the client is feeling suicidal. The client and therapist work together to identify adaptive responses that can be used to counter the maladaptive or unhelpful beliefs when the client is in crisis. The content of these maladaptive core beliefs and adaptive responses are put on wallet-sized coping cards that are easily accessible to the client. During this phase, the client creates a hope kit, which includes content associated with the client's reasons for living (e.g., photos). The therapist also teaches the client behavioral coping skills during this phase. These are activities that help the client to manage suicidal thoughts and urges for suicidal behavior (e.g., distraction, self-soothing activities).

The final three sessions are focused on relapse prevention. At this point the client has gained an understanding of maladaptive core beliefs that lead to suicidal thoughts and has had opportunities to begin using strategies such as the coping card, hope kit, and behavioral coping skills to manage suicidal thoughts and urges for behavior. During the last three sessions the therapist's primary goal is to ensure that the client uses these skills during future suicidal crises. To assess this, the therapist guides the client through an imagery task in which the client imagines the thoughts, feelings, and events that lead up to a suicide attempt. The client then imagines him or herself effectively using the skills he or she has learned in therapy and describes this to the therapist. This description is used by the therapist to determine the client's mastery and likelihood of success in future situations associated with suicide risk.

The treatment described above was evaluated by Brown and colleagues (2005) in a randomized controlled trial. Participants in this study were 120 adults who had attempted suicide and were evaluated in the emergency department within 48 hours following the attempt. Participants were randomized to cognitive therapy or usual care. Follow-up evaluations conducted 18 months following the baseline evaluation indicated that 24% of those in the cognitive therapy condition compared to 41.6% of those in usual care made at least one suicide attempt, indicating a significantly lower reattempt rate. In addition, self-reported depression was significantly lower in the cognitive therapy participants at 6, 12, and 18 months, and hopelessness was significantly lower at 6 months.

Collaborative Care and Collaborative Assessment and Management

A number of studies have also examined approaches to the reduction of suicide risk via reductions in depression, hopelessness, and suicide ideation, among others. These studies have included a variety of populations, including college students, older adults, and inpatients, among others (Alexopoulos et al., 2009; Bruce et al., 2004; Jobes, Kahn-Greene, Greene, & Goeke-Morey, 2009; Jobes, Wong, Congrad, Drozd, & Neal-Walden, 2005; Unützer et al., 2002, 2006). A broad review of this literature is beyond the scope of this chapter; however, we discuss the outcomes of studies using collaborative care programs, as well as the Collaborative Assessment and Management of Suicidality (CAMS; Jobes, 2006), an approach that can be used to target suicide risk in patients who might go on to participate in another form of treatment for a primary Axis I disorder such as MDD.

Older adults with depression are more likely to discuss their concerns with a primary physician than a mental health practitioner (Luoma, Martin, & Pearson, 2002). As such, it is necessary for primary care environments to include care managers or other individuals knowledgeable about depression, suicide risk, and other psychological difficulties. In recent years, several studies have examined the benefits of including collaborative care for older adults being treated for depression in primary care, with a focus on reducing suicide ideation and depression (e.g., Alexopoulos et al., 2009; Bruce et al., 2004; Unützer et al., 2002, 2006). One such example is the Improving Mood: Promoting Access to Collaborative Treatment (IMPACT) trial (Unützer et al., 2002, 2006). Adults 60 and over (N = 1,801) were randomized to care as usual (antidepressant medication or counseling) or a collaborative care program that included a depression care manager and the primary care physician (Unützer et al., 2006). The depression care manager provided education about treatment options, encouraged clients to engage in behavioral activation, and allowed clients to choose between antidepressant medication and a problem-solving treatment. The client met with the depression care manager every two weeks during the acute phase of treatment and then monthly during the continuation phase. Participants were evaluated at baseline, 3, 6, 12, 18, and 24 months. Importantly, participants randomized to the intervention reported significantly lower suicide ideation and thoughts of death at all assessment points (Unützer et al., 2006).

Jobes (2006) developed the CAMS treatment approach for suicide risk that includes an emphasis on assessment as well as treatment. CAMS emphasizes a collaborative understanding of the key factors that contribute to suicidal desire, such as psychological pain, stress, agitation, hopelessness, and self-hated. Further, the therapist and patient evaluate suicide risk through an examination of reasons for living and dying, as well as known risk and protective factors for suicidal behavior. Following early steps that build understanding and a strong therapeutic relationship between therapist and client, an initial suicide-specific problem-focused treatment plan is developed to target key concerns related to suicide risk. Importantly, the CAMS approach may be used as an initial approach to treatment for patients with MDD who have elevated suicide risk. Although no studies to date have specifically examined outcomes for patients with MDD, existing studies suggest that patients treated with CAMS experience reduced suicidal desire (e.g., Jobes et al., 2005, 2009) and inpatients treated with CAMS (open-trial) experience significant reductions in depressive symptoms, hopelessness, suicide ideation, suicide cognitions, and factors that drive suicide risk (Ellis, Green, Allen, Jobes, & Nadorff, 2012).

Conclusions

Although this chapter has provided the reader with a wealth of information related to suicide risk and death by suicide, it is clear that much is missing from the literature. Perhaps most daunting is the significant need for treatment approaches that reliably lead to reductions in death by suicide. As noted above, very few studies have been able to claim this, suggesting a critical need for intervention approaches that address a variety of risk factors, are theoretically based, and can be applied in a variety of settings likely to service adults at risk for suicide. A variety of challenges confront practitioners working with suicidal clients, including fatigue and burn-out, anxiety about litigation, and a human concern about being able to help those at risk for suicide. Despite these challenges, we hope that the future brings a burgeoning literature on this topic filled with approaches that will lead to fewer lives lost to suicide.

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CHAPTER

17 Comorbidity of Bipolar Disorder and Depression

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Abstract

There has been speculation about the relationship between depression and mania for centuries. Modern psychiatry and psychology have mostly viewed these as different subtypes within a "family" of mood disorders. Conceptual models of comorbidity provide an opportunity to re-examine the association between depression and other pathological mood states. We examine the evidence pertaining to rates of "comorbidity," which, in this case, refer to the lifetime occurrence of depression and hypomanic, mixed, or manic episodes in the same individual. We explore factors that could contribute to artifactual comorbidity. We also examine data pertaining to similarities or differences in phenomenology, longitudinal course, associated features, family history, and treatment response. Multiple factors are likely involved in the comorbidity of depression and hypomania or mania, and the problems of poor reliability and inconsistent diagnostic definitions and methodology attenuate the significance of most research findings. However, evidence appears sufficient to conclude that not all depression is on the bipolar spectrum, that bipolar features moderate the course and outcome of depressive illness, and that depression and bipolar disorder most likely involve a blend of some shared and some specific mechanisms. Research and clinical work both will advance substantially by more systematically assessing for potential bipolar features "comorbid" with depression and following how these factors change the trajectory of depression over time.

Key Words: bipolar disorder, mania, hypomania, mixed episodes, depression, comorbidity

For thousands of years, observers of human behavior have noted a possible connection between people experiencing intense mania and severe depression. Aretaeus of Cappadocia (now Turkey) is credited as the first person to write that mania might be an extreme form of depression, more than 1500 years ago (Glovinsky, 2002). Kraepelin went further, lumping most forms of mood disorder together into a broad category of "manic depressive insanity," distinct from dementia praecox, or what is now known as schizophrenia. In Kraepelin's view, even people experiencing recurrent episodes of depression without ever developing mania still were struggling with a variant of manic depression (Kraepelin, 1921).

However, other clinicians noted that many people with depression had no history of mania, either in their personal past, or in their families. Even following them over the course of years or decades, they never blossomed into a mania. Two landmark studies conducted simultaneously in Europe carefully investigated family histories, finding that depression and variations of mania appeared to each breed true (Angst, 1966; Angst, Felder, Frey, & Stassen, 1978; Perris, 1966). Some families only showed histories of depression, whereas others displayed blends of depression and mania. On the basis of these and subsequent studies, the *Diagnostic and Statistical Manual* (*DSM*) of the American Psychiatric Association separated

unipolar depression from manic depression, renaming the latter "bipolar disorder" to emphasize that the condition could be marked by either extreme form of mood disturbance (American Psychiatric Association, 1968; Goodwin & Jamison, 2007). The unipolar/bipolar distinction has been retained in all subsequent revisions of the *DSM*, and unipolar depression has become much more widely diagnosed than bipolar disorder. Some argue that the pendulum has swung too far, and longitudinal studies suggest that a substantial portion of cases diagnosed with depression prove to have a bipolar form of illness when followed prospectively (Angst et al., 2011; Angst et al., 1978; Fiedorowicz et al., 2011). The boundary between unipolar depression and bipolar disorder also remains unclear, as clinical presentations such as agitated depression and mixed mood states defy attempts at neat categorization.

Although the distinction has fascinated academicians, clinicians could be forgiven for asking if the delineation of bipolar from unipolar depression has practical consequences. Does it matter if a person has a history of mania or hypomania "comorbid" with the depression for which they are seeking help? In the case of comorbid mania, few would argue that the periods of elevated mood are without impairment or the need for treatment. However, the question becomes more pointed in the case of hypomania: If people have periods of increased energy and elevated mood, but it is not causing them impairment, and they are not asking for help managing their hypomania, then why go to the effort of evaluating it? Why stigmatize periods of higher functioning by labeling it as a bipolar disorder rather than depression?

We have argued that clinical assessment is not an end of its own, but rather a means to improved treatment. From that viewpoint, additional assessment or a diagnostic distinction is warranted if it addresses one of the "3 Ps" of *predicting* important criteria, *prescribing* a change in treatment, or informing the *process* of managing the condition and measuring outcomes (Youngstrom, 2008). We will examine different theoretical models of the relationship between depression and manic or hypomanic symptoms, and then critically evaluate whether the body of evidence justifies attending to a range of bipolar features that appear comorbid with depression.

Models of the Relationship Between Depression and Bipolar Disorder

Unipolar as a Subtype of Bipolar

In Kraepelin's (1921) model, manic-depressive insanity was a broad category that subsumed a wide variety of different clinical presentations. In addition to what we would now call bipolar I disorder, Kraepelin's classification lumped together recurrent unipolar depression with other bipolar forms of illness. Kraepelin acknowledged that some people responded to stressful events with a depressed-looking reaction, but he believed that if the depression did not recur, it was likely to reflect a different etiology and course—foreshadowing the later distinction between endogenous and reactive subtypes of depression (Brown & Harris, 1978).

The immediate and strong challenge to lumping all mood disorders together was the observation that many people only experienced depression. The greater prevalence of depression, coupled with the fact that people are much more motivated to seek help when depressed, led many experts to advocate "splitting" depression away from manic-depression.

Bipolar as a Subtype of Mood Disorder

The inverse model, that bipolar disorder is a subtype of a mood disorder, also has deep historical roots, with theoreticians arguing that mania might be an extreme form of depression, or a defensive reaction to extreme depression. The same counterargument applies here. Just as cases manifesting only unipolar depression challenged the argument that all depression belonged under the bipolar rubric, examples of unipolar mania refute the argument that all manic presentations are a subset of depressive disorders (Solomon et al., 2003; Yazici et al., 2002).

A difficulty with both of these models is that mood disorders are episodic conditions, and the correct diagnosis can change in light of a new episode. A manic episode at any point in life necessitates a *DSM* diagnosis of bipolar I, regardless of whether there has been an episode of depression (American Psychiatric Association, 2000). A hypomanic episode following an episode of depression changes the diagnosis from unipolar depression to bipolar II and remains even if another hypomanic episode never occurs. The only way to be sure about an individual's diagnosis is to follow the person for the course of his or her entire life, and even then, there might be cases of latent mood disorder that had not manifested. An analogy could be made to cancer, with which people usually become aware of the illness when it is causing problems, and with which it might episodically recur in later years. People might die of other causes, only to have "silent" tumors be revealed on autopsy (Goldman

et al., 1983). In similar manner, bipolar disorder may go undetected unless the signature symptoms cause problems. Many people seek treatment first for their depression, and either never had a prior hypomania or mania, or decided that the hypomania was not worrying enough to be worth reporting. Others may experience their first hypomania or mania years after their initial depression, only then revealing that theirs was a bipolar illness.

Epidemiological studies are now trying to model lifetime rates more accurately to account for "conversion" from unipolar depression to bipolar disorder over time, sometimes also adjusting for premature mortality (Merikangas & Pato, 2009). Longitudinal studies are moving toward using "event history" approaches such as survival analyses or Cox regression (Tabachnick & Fidell, 2007). These techniques explicitly change the question from "Yes or no, does the person have bipolar disorder?" to "How long until they have an episode?" Another advantage of the event-history approaches is that they allow "censoring" of data, where cases that have not converted are treated as "not yet bipolar, and maybe never; but perhaps they would develop it later." These models better reflect the inherent ambiguity of working with episodic conditions that may have different phenomenological presentations.

Unipolar mania appears rarer in the United States than unipolar depression, but it still appears to occur. Clinical studies tend to find that fewer than 20% of adults with bipolar I have histories devoid of major depressive episodes; however, often these cases still have some milder depressive symptoms (Goodwin & Jamison, 2007). It is possible that unipolar mania might be more associated with hyperthymic temperament (Perugi et al., 1998). Mania first occurring in late life and absent a family history of bipolar disorder appears more likely to have a different, organic etiology (Moorhead & Young, 2003). The rarity in clinical settings and the difficulties in documenting a purely manic course of illness have led some experts to question whether unipolar mania is a distinct entity (Goodwin & Jamison, 2007). However, epidemiological studies in nonclinical community samples find higher rates of unipolar mania than reported in clinical samples (Merikangas et al., 2012). This discrepancy is at least partly due to selection bias in treatment seeking. Not only are people more likely to seek mental-health services when depressed, but mania is associated with increased risk of incarceration and accidents, which may distract from identifying the underlying illness (Quanbeck et al., 2004; Stewart et al., 2012). Regardless, unipolar mania appears sufficiently common that a model positing mania as a subtype of depressive disorder does not seem tenable.

Bipolar as a Completely Independent Condition

A third model posits that bipolar disorder is a condition independent of unipolar depression. There are two variants of this model. One might focus on mania or hypomania as an independent condition. This would set up a 2 × 3 table, with six possible cells (see Table 17.1). What was considered classic manic-depression would be conceptualized as the comorbidity of a manic disorder and a separate depressive disorder. This model also would expect to see unipolar mania and unipolar depression, as well as people who experienced neither condition. If the manic disorder and depressive disorder were etiologically independent conditions, then the expected rate of co-occurrence, or comorbidity, would be the product of each of their own rates in the population. For example, if depressive disorders affected 20% of a population and manic disorders affected 5%, then the rate of mania comorbid with depression would be predicted at 5% * 20% = 1% of the sample (Caron & Rutter, 1991). The observed rates

Table 17.1 Patterns of Occurrence of Manic and Depressive Episodes

		Mania	
	Mania	Hypomania	Absent
Depression			
Present	Bipolar disorder (Bipolar I)*	Bipolar II*	Unipolar depression (Major depressive disorder)*
Absent	Unipolar mania (Bipolar I)*	No diagnosis, or bipolar not otherwise specified	No mood disorder

* DSM-5 proposes a "mixed" specifier that could be coded when both hypomanic and depressive symptoms are present much of the time during the same episode.

of hypomania and mania comorbid with depression are generally significantly higher than would be predicted if these were completely independent disorders.

A second variant of the separate-conditions model would be that there are multiple pathways leading to a depressed phenotype. In this model, unipolar depression might reflect a phenomenological endpoint resulting from one set of risks and processes. The depressed presentation of a bipolar disorder could be a similar-appearing outcome of a different set of risks and processes. This could be described as a phenocopy, in whixha phase of bipolar illness mimics the presentation of unipolar depression, or it could be construed as an example of equifinality in developmental psychopathology, in which a different diathesis or mechanism leads to a similar convergent outcome (Cicchetti, 1992). If bipolar depression appears different from unipolar depression, that would support the idea that these are distinct disorders. Similarly, if specific risk factors or mechanisms were associated with nonshared aspects of the depressive phenotypes, that would also lend support to the different distinct-conditions models. The strong version of the independent-conditions model would predict that there is no bipolar depression, only a unipolar depression that is comorbid with a manic disorder. In this case, there would not be any features of the depression that change based on whether there is a history of hypomania or mania, because depression is a separate entity from the comorbid conditions.

Mania and Depression as Two Continua

There has been a resurgence of interest in dimensional models of psychopathology in general (Kraemer, 2007), and an increased emphasis on dimensional ways of describing disorders in *DSM*-5. The majority of the evidence suggests that dimensional approaches more accurately reflect the distribution of depressive and manic symptoms in clinical and nonclinical samples (Haslam, Holland, & Kuppens, 2012). Most statistical investigations of the structure of depressive symptoms find that dimensional models fit the data better (Prisciandaro & Roberts, 2005; Ruscio & Ruscio, 2002) although there are exceptions (Ruscio, Zimmerman, McGlinchey, Chelminski, & Young, 2007). Less work has been done with bipolar disorder; but again, the preponderance of evidence supports dimensional (Perez Algorta, Youngstrom, Frazier, & Findling, 2008; Prisciandaro & Roberts, 2011) instead of categorical models (cf. Ahmed, Green, Clark, Stahl, & McFarland, 2011).

If manic and depressive symptoms are both dimensional, then what is the degree of association between the dimensions? One possibility is that depression and mania might be opposite ends of a bipolar continuum, where "bipolar" refers to a dimension anchored by polar opposites instead of the presence or absence of a single quantity (Russell & Carroll, 1999). However, the frequently observed phenomenon of mixed mood states, blending symptoms of both mania and depression contemporaneously, contradicts the single dimension bipolar model. Mixed presentation also suggests a positive correlation between the depressed and manic symptoms, rather than a negative correlation suggested by state versus trait investigations of self-reported emotion (Carroll, Yik, Russell, & Barrett, 1999). Studies of hypomanic symptoms and depression often find the two dimensions correlate to a moderate or large degree in clinical samples (Danielson, Youngstrom, Findling, & Calabrese, 2003; Depue et al., 1981; Youngstrom, Findling, Calabrese, et al., 2004), but still significantly lower than would suggest that they are driven by the same underlying factor.

One way of reconciling these apparently disparate findings is to divide mania and depression into component processes and elements. Mood disorder involves aspects of cognitive and somatic disturbance as well as extreme affective experiences (Kraepelin, 1921), and these need not all be activated or impaired at the same time. Within the affective realm, there are emotions that are probably opposite poles from each other (happiness and sadness being a well established example) that are unlikely to occur simultaneously (Carroll et al., 1999), but which could occur sequentially or at isolated extremes during the course of a mood disorder. On the other hand, affective neuroscience indicates that anger may share more in common with reward pursuit, social dominance, triumph, and other approach-oriented emotions that may have neutral or positive valence (Demaree, Everhart, Youngstrom, & Harrison, 2005). Put another way, science is suggesting that mixed states are more likely to be highly activated and approach oriented, characterized by more irritability and less nostalgia or wistfulness (low energy, bittersweet mixed emotions; Youngstrom, 2009).

Integrating affective neuroscience into a model of mood disorder results in two correlated affective dimensions of depressive and manic symptoms. The

positive correlation between them is stronger when viewed from a longitudinal or trait perspective, because some aspects that would appear antagonistic at a state or momentary analysis level (e.g., being happy and sad at the same time) can unfold over distinct episodes. Bipolar disorder does not result in contradictory moods at the same time, but, rather, it may be a propensity to experience extremes of emotion, with a greater variation of mood over time than found in those with unipolar depression (Lovejoy & Steuerwald, 1995). Temperament or personality may fill an intermediate position on the continuum, with depressive temperament or emotional instability overlapping with low-level depressive symptoms, and also constituting a diathesis establishing vulnerability for more extreme mood states (see Figure 17.1).

In an integrated dimensional model, mixed mood states could also involve blends of emotions that share strong activation components. Anger is an excellent example of an approach-oriented, highly activated emotion that shares much in terms of cortical activity with other approach-oriented emotions and states (Harmon-Jones & Allen, 1998), such as exuberance and reward seeking (Johnson & Jones, 2009). The relative "proximity" of anger to other high activation, approach-oriented emotions suggests that similar stimuli might elicit anger and frustration in the context of goal-pursuit, and that it is a shorter neural and emotional distance to travel between euphoria and rage compared to euphoria and sadness, or rage versus boredom. Modern neuroscience is exposing a basis for the clinical observation that it is more common to see shifts between intense emotions with different valences, rather than blends between polar opposites on the affective circumplex (Carroll et al., 1999; Rich et al., 2011).

Affective Temperament: Substrate, Diathesis, or Moderator of Depression?

Research suggests that the nature of one's temperament, the biological underpinnings of affect, is a key risk factor in the development of mood disorders. Of the five affective temperament styles—cyclothymic, hyperthymic, anxious, irritable, and

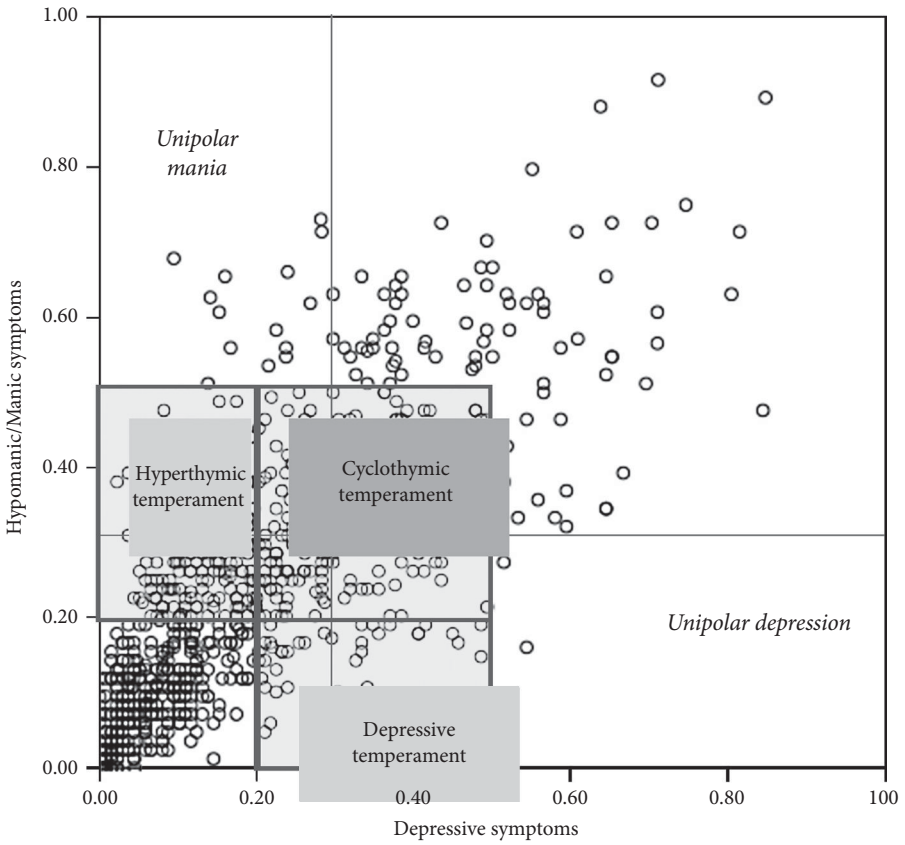

Figure 17.1 Schematic mapping of affective temperament and dimensions of mood symptoms.

depressed—cyclothymic temperament, characterized by shifts in mood, interests, and energy, and by changes in confidence, sleep patterns, and relationships (Akiskal, Khani, & Scott-Strauss, 1979), in particular, is thought to be one of the strongest predictors of bipolar disorder (Akiskal, 1996; Akiskal et al., 1985; Depue, et al., 1981; Hantouche & Akiskal, 2006; Klein, Depue, & Slater, 1986; Kochman, et al., 2005; Oedegaard, Syrstad, Morken, Akiskal, & Fasmer, 2009).

Affective temperament is thought to be largely driven by genes (Evans et al., 2008; Greenwood, Akiskal, Akiskal, & Kelsoe, 2012), resulting in a traitlike manifestation of the namesake characteristic (Evans et al., 2005). Individuals who have this affective foundation, may be at greater risk for related symptomatology. Temperament also influences the way in which an individual interacts with the world, sculpting—to some extent—later exposure to risk and/or protective factors (Izard, 2007; Rothbart & Posner, 2006). Depending on the circumstances, this may lead to a more or less severe presentation of affective symptomatology.

Affective temperaments are sometimes conceptualized as diathesis for mood disorder (Rihmer, Akiskal, Rihmer, & Akiskal, 2010), and other times as moderating factors that, when comorbid with depression, can significantly alter presentation of the mood disorder (Akiskal, 1996; Kochman et al., 2005; Mendlowicz et al., 2005). The latter conceptualization is sometimes described as "soft bipolarity" (Akiskal, 2003; Angst, et al., 2003; Goto, Terao, Hoaki, & Wang, 2010). Of greatest interest in a chapter about comorbidity is the combination of major depression with comorbid cyclothymic temperament, because it may represent a transitional zone between unipolar depression and bipolar spectrum illness (bipolar II 1/2; Akiskal & Pinto, 1999).

Temperament may not always "match" a person's primary psychopathology; depression superimposed on an affective temperament changes its quality/character. For example, a cyclothymic temperament, coupled with depression, may manifest in low mood combined with greater mood instability, irritability, treatment resistance, social impairment, agitation, restless energy, plus a high conversion rate to bipolar disorder (Mendlowicz et al., 2005). People with an anxious temperament also develop high rates of depression, again suggesting imperfect specificity of temperament for acute diagnoses.

Both hyperthymic and cyclothymic temperament predict manic episodes, but, interestingly, the association is stronger with cyclothymic temperament despite its more mixed content. A simplistic model—pathology as extreme expression of temperament—would hypothesize that mania would be an exacerbation of hyperthymic temperament instead of cyclothymic. However, in a large epidemiological study, cyclothymic temperament was a stronger marker for bipolar disorder, with a specificity of 88% (Hantouche et al., 1998). In a prospective study of adults with depression, characteristics associated with cyclothymic temperament, including mood lability and excessive energy, were predictive of conversion to bipolar disorder, and of an earlier age of onset of depression (Akiskal et al., 1995). Similarly, cyclothymic temperament differentiates between unipolar and bipolar depression *before* the onset of [hypo]mania (Mendlowicz et al., 2005). Given that 20–40% of youth with depression will go on to develop bipolar disorder, identifying risk factors for mania, like cyclothymic temperament, among depressed youth is important.

Epidemiological studies suggest that, whereas the prevalence of the DSM-defined subtypes of bipolar disorders is likely between two and three percent (Angst et al., 2010; Merikangas et al., 2011), the number of people who meet criteria for major depression, plus a cyclothymic or hyperthymic temperament, is much higher. In assessing only for depression or mania, as prescribed by the DSM, we underestimate not only the rate of comorbid depression and cyclothymic symptoms (Goto, Terao, Hoaki, & Wang, 2010), but also the impairment caused by these subthreshold presentations (Angst et al., 2011).

Unfortunately, affective temperament is rarely assessed clinically. Though cyclothymic temperament is associated with considerable risk for substance use and self harm, as well as mood disorder, hyperthymic temperament, characterized by increased energy, productivity, confidence, and sociability, is thought of as largely positive and, in a depressed individual, may offer increased mood reactivity and energy, helping to counteract some of depression's key features. In adults with major depression, those who had a comorbid hyperthymic temperament had a later age of onset and hospitalization than those with cyclothymic temperament, had fewer episodes than other depressed individuals (regardless of temperament), and had lower rates of hypomania than others (Akiskal, Lancrenon, & Hantouche, 2006). Importantly, individuals with hyperthymic temperament also had much lower rates of family history of psychiatric hospitalization, suicide attempt, completed suicide, depression, and

bipolar disorder, suggesting that their future risk for negative outcomes was also lower than that of depressed individuals with other affective temperament styles or that of depressed individuals without an affective temperament (Akiskal et al., 2006).

On the other hand, cyclothymic temperament, comorbid with depression, may enhance the negative aspects of depression, such as restlessness, irritability, and social problems. Because the symptoms of cyclothymic temperament are often similar to those seen not only in depression but also in other disorders, failure to recognize the temperament and its effect on the phenomenology of depression is common. Unfortunately, not assessing temperament limits the opportunity to treat it, independent of the depression, and misses the potential to mitigate the risk conferred by temperament for the onset of mania later on (Mendlowicz et al., 2005).

Opportunities for the prevention of hypomania or mania are best in young people. Research suggests that the index episode of bipolar disorder is usually depression, particularly in young people (Hillegers et al., 2005; Strober et al., 1995). For that reason, the identification of a cyclothymic temperament in a youth is especially important. In a study of 109 youth from a inpatient psychiatric hospital, all of whom met criteria for major depression, 64% of those who met criteria for cyclothymic temperament had experienced an episode of hypomania or mania at the end of a two-year follow-up (Kochman et al., 2005). In contrast, only 15% of youth without cyclothymic temperament had a hypomanic or manic episode. In multiple studies of adults with major depression, cyclothymic temperament was associated not only with an earlier age of onset of depression (Mendlowicz et al., 2005), but also with greater risk for other factors associated with bipolar disorder, including a family history of bipolar disorder (Akiskal, et al., 2006; Maina, Salvi, Rosso, & Bogetto, 2010).

Cyclothymic temperament, in addition to increasing the likelihood of mania in a person with depression, may also result in a more severe course of illness (Cassano et al., 1999; Koukopoulos et al., 2006; Mendlowicz et al., 2005). Youths with cyclothymic temperament had an average of 2.3 depressive episodes, and 3.5 [hypo]manic episodes over the course of two years, whereas those youth with depression, but not a cyclothymic temperament had an average of 1.3 depressive episodes, and less than 0.5 [hypo]manic episodes (Kochman et al., 2005). Youth with cyclothymic temperament also have greater clinical, social, and interpersonal impairment than those youth without cyclothymic temperament. Similarly, in a study of adults presenting with depression, those with cyclothymic temperament had an early onset, higher mood instability, more rapid switching between mood polarities, greater irritability, and more suicidality (Akiskal et al., 2006). Depression was comorbid with cyclothymic temperament in one-third of cases, and "BP II ½" was both the most prevalent and impaired expression of the bipolar spectrum (Akiskal et al., 2006).

The severity of expression associated with comorbid cyclothymic temperament and depression may be due, in part, to the complicated clinical picture. In a study of adults with depression, cyclothymic temperament was associated with increased likelihood of other psychiatric disorders, including panic disorder, bulimia nervosa, alcohol disorders, and borderline personality disorder (Perugi, Toni, Travierso, & Akiskal, 2003). This group of individuals may also have fewer resources from which to draw support due to lower quality of relationships, interpersonal sensitivity, and functional impairment (Perugi et al., 2003). The lack of social support and the volatility of interpersonal relationships complicates prognosis and may interfere with therapy.

Depression is strongly associated with suicide, and, unfortunately, cyclothymic temperament increases that risk. Among depressed youth, 81% of those with cyclothymic temperament had at least one episode of suicidal ideation, whereas 36% of those without cyclothymic temperament reported suicidality (Kochman et al., 2005). Similar patterns have been found in studies of adults; importantly, though cyclothymic temperament increases risk for suicide, hyperthymic temperament is protective (Pompili et al., 2012; Rihmer, et al., 2009).

Cyclothymic temperament may also make treatment of depression more complicated. Though the data on whether antidepressant use can incite an episode of mania (Joseph, Youngstrom, & Soares, 2009) are inconclusive, studies have shown that a cyclothymic temperament makes it more likely that antidepressant use will coincide with the onset of [hypo]mania in a person with depression (Akiskal, Djenderedjian, Rosenthal, & Khani, 1977; Kochman et al., 2005; Maina et al., 2010). This highlights the importance of assessing for cyclothymic temperament in depressed patients. Even if they do not have a [hypo]manic episode related to antidepressant use, individuals with a cyclothymic temperament are less likely to respond well to traditional therapies, and may require a mood stabilizer or atypical antipsychotic (Maina et al., 2010).

In summary, the presence of cyclothymic temperament, comorbid with major depression, represents significant risk for an earlier age of onset of depressive symptoms and a more persistent course of illness. Though cyclothymic temperament is not associated with symptoms as severe as those seen in [hypo]mania, research suggests that it is the best predictor of bipolar disorder, and that it may offer the best opportunity to identify and intervene with those at risk. However, even for those who do not progress to develop [hypo]mania, cyclothymic disorder with depression is associated with increased impairment across a number of constructs, including episode duration and frequency, treatment resistance, comorbidity, interpersonal relationships, and suicidality. Assessment of temperament, particularly for those with an early onset of depression may provide important information related to the course, outcome, and treatment of the disorder.

Due to the state of development of the literature, it is premature to draw final conclusions about the role of temperament with regard to depression and bipolar disorder. The idea that temperament is a precursor of mood disorder has not been tested in prospective studies of youths. Measures of affective temperament have been used almost exclusively in adult samples, and the temperament constructs investigated in children have independent theoretical histories (Carey, 1998; Chess & Thomas, 1989; Kochanska, 2001; Rothbart & Posner, 2006) and rarely have been investigated in the context of adults or clinical samples, let alone with formal psychiatric diagnoses of mood disorder. There have been recent efforts to map the constructs so that there are links between various models of temperament, personality, and psychopathology (Shiner, Tellegen, & Masten, 2001), but without prospective data there cannot be a decisive resolution about whether temperament antedates mood disorder. New data are also needed to clarify whether mood disorder is best considered a dysfunctional extremity along a continuum of normative temperament, versus a pathological aggravation of a dispositional style. The available evidence already supports the value of temperament as a moderating variable for concurrent and prospective correlates of depression.

Behavioral Activation and Behavioral Inhibition: Risk Factor or Symptom for Mania and Depression?

An intriguing idea, explored in the literature, is that dysregulation of the behavioral activation (BAS) and behavioral inhibition (BIS) systems contributes to both the manic (high BAS, low BIS) and depressive (high BIS, low BAS) symptoms of bipolar disorder. The BAS is thought to govern approach emotions, motivation, and positive mood states (Carver & White, 1994). When overactive, the BAS may lead to a variety of psychopathology, including conduct disorder, antisocial personality disorder, and mania (Johnson, Turner, & Iwata, 2003). The BIS, on the other hand, inhibits impulses, and leads to avoidance; in excess, it is associated with depression and anxiety (Johnson et al., 2003). The two systems are independent and, depending on the function of each system, the associated characteristics can be tempered or exacerbated.

A classical depression is expected to be accompanied by a high BIS, resulting in worry and avoidance, as well as low BAS, leading to a lack of motivation, energy, and positive mood. In contrast, a low BIS could exacerbate the disinhibition and approach of mania, particularly when combined with a high BAS. In the case of a high BIS and a high BAS, a mixed state might be expected, and with alow BIS and a low BAS, a nonpathological state of boredom characterized by low levels of anxiety and low motivation (Depue & Iacono, 1989; Matthews & Gilliland, 1999; McFarland, Shankman, Tenke, Bruder, & Klein, 2006). Research has produced inconsistent results regarding the nature of these relations, in particular whether one's BIS and BAS are traitor statedependent (Meyer, Johnson, & Winters, 2001). Thus, though evidence suggests that a high BIS is a risk factor for depression and that a high BAS creates a vulnerability to mania, it is not clear whether the elevations in BIS and BAS found during mood episodes have clinical utility as predictive factors for disordered mood. It may be that a better conceptualization is that the BIS/BAS dysregulation is a symptom of the pervasive nature of these mood states.

ADDITIONAL ISSUES IMPLIED BY DIMENSIONAL MODELS

Dimensional models of depressive and hypomanic/manic symptoms suggest an intriguing range of possibilities in terms of the relationship between mood and functioning. Depressive symptoms correlate negatively with quality of life or global functioning (Judd et al., 2000). Hypomanic and manic symptoms also reduce functioning and quality of life, but to a lesser degree than depressive symptoms do (Freeman et al., 2009; Michalak, Yatham, Maxwell, Hale, & Lam, 2007). Hypomania may actually have a positive effect compared to mania

or depression, suggesting either a curvilinear relationship analogous to the "optimal level of arousal" model (Yerkes & Dodson, 1908), or else a buffering effect, whereby the energy and activity associated with hypomania might compensate for some of the negative features of depression (Freeman et al., 2009). Because most work has operationalized "mixed mood" as an episode or categorical state (e.g., denoted by the presence or absence of a specifier; American Psychiatric Association, 2000), it is unknown whether an interaction effect between the two mood dimensions might provide a more parsimonious description of their complex associations with functioning.

Pseudo Comorbidity

There are several factors that will contribute to the appearance of comorbidity between bipolar disorder and unipolar depression. These are not just of academic interest. Many of these pitfalls beset clinical practice. Raising awareness about them can improve care as well as strengthen research designs.

POOR RELIABILITY OF BIPOLAR DIAGNOSES

The reproducibility of diagnoses is often low, especially when relying on unstructured clinical interviews. A recent meta-analysis found that the typical kappa (agreement above chance levels) for clinical diagnoses and structured interview diagnoses was only 0.27; however, it was worst for diagnoses of bipolar disorder, with an average of $K = 0.08$ (Rettew, Lynch, Achenbach, Dumenci, & Ivanova, 2009). Clinicians often conceptualize cases differently, and one's prototype for bipolar II is another's exemplar of agitated depression. Using a consistent set of definitions, using more structured or systematic approaches to eliciting symptoms, and being alert to cognitive biases (Croskerry, 2002; Youngstrom, Freeman, & Jenkins, 2009) all can improve diagnostic accuracy.

SPURIOUS COMORBIDITY

There also are more granular factors that can increase apparent rates of comorbidity. One is overlap in symptom criteria. Irritable mood is a symptom that can count toward either mania or depression, in both *DSM-IV* (American Psychiatric Association, 2000) and the proposed criteria for *DSM-5* (American Psychiatric Association, 2012). Similarly, motor agitation can be a common symptom of depression, difficult to distinguish from the increased motor activity of mania; and poor concentration in depression could be confused with distractibility in mania if the symptoms were not considered in the larger context of associated symptoms and features. These three symptoms also are included in a variety of other diagnoses, such as generalized anxiety disorder, post-traumatic stress disorder, and attention-deficit/hyperactivity disorder (American Psychiatric Association, 2000). If the clinician simply counts the number of symptoms endorsed on a checklist, or credits the endorsement of a symptom to each possible diagnosis, then this will make it easier to meet criteria for apparently comorbid diagnoses. If irritable mood, motor agitation, and impaired concentration are applied indiscriminately toward other diagnoses, then a person with a major depressive episode would only need to endorse two other manic symptoms (out of five remaining criteria in section B of the criteria for manic episode,) to meet threshold for mania, and only three more symptoms to meet criteria for a "comorbid" attention-deficit/hyperactivity disorder (Youngstrom, Arnold, & Frazier, 2010). Research interviewers and clinicians differ in their training about how to best find a diagnostic home for each symptom, and how to tease apart potential comorbid presentations, contributing to the large differences in rates of comorbidity estimated across studies and clinics (Kowatch, Youngstrom, Danielyan, & Findling, 2005).

A related artifact would be counting symptoms that happened in separate episodes, perhaps months or years apart, toward a given diagnosis. Our informal nickname for this is constructing a "Franken-episode," alluding to Shelley's monster that was stitched together out of pieces from separate entities. Borrowing symptoms from different events or times makes it much easier to meet criteria for a pseudo-disorder. However, efforts to emphasize co-occurrence can overcorrect and reduce the sensitivity of rating scales and possible interviews (Miller, Klugman, Berv, Rosenquist, & Ghaemi, 2004; Wagner, et al., 2006). Optimally, methods emphasize co-occurrence sufficiently to avoid false positives confabulated from different events and settings, without raising the bar so high that real mood episodes are missed.

This issue of potential "double counting" of symptoms is important to the *DSM-5* proposal to drop mixed-mood episodes and add a mixed-mood specifier, instead. The specifier could be coded to denote a pronounced mixed presentation during a manic, hypomanic, or depressed episode. The proposed criteria for the mixed specifier are complicated, as they attempt to avoid relying on symptoms

that could easily be construed as present during simple mania or depression. The mixed specifier definitely changes which cases would be classified as having a mixed presentation (Algorta et al., 2011). It remains to be seen whether the criteria are feasible for use in routine clinical work or research.

Another source of variation is the hierarchical arrangement of some diagnoses within the DSM nosology. Mood disorder and schizophrenia are the top ranking diagnoses in the hierarchy. If diagnostic classification were organized as a card game, then mania and schizophrenia would be the trump cards that take precedence over any other diagnosis. If the diagnostic criteria for mania are satisfied, at any point in the person's life, then the diagnosis changes to bipolar I; and if the person shows impairments in attention, impulsivity, or anxiety, these other issues must occur outside of the context of a mood episode in sufficient amount and severity to warrant a separate diagnosis, or else these symptoms are subsumed under the mood disorder (even though the symptoms are not all themselves considered required symptoms for mania or depression). These hierarchical exclusions have a big impact on rates of anxiety disorders and impulse control disorders diagnosed as comorbid conditions on top of a mood disorder (Mineka, Watson, & Clark, 1998). Strictly applying the hierarchical exclusions generates much lower apparent rates of comorbidity. The hierarchical relationships between unipolar depression and hypomania or mania are not fully clarified in the current versions of the DSM, and there are cases whose phenomenology does not fit neatly into the defined categories, consistent with a more dimensional formulation.

PRESENTING PROBLEMS AND PATTERNS IN TREATMENT SEEKING

The effects of low reliability of diagnostic methods are exacerbated by trends in the way that individuals seek treatment and describe their concerns. People are most motivated to seek treatment when they are depressed and anxious. When the same person is manic, the individual is unlikely to seek help and may be more likely to get arrested or have an accident requiring medical care. Hypomania is, by definition, not impairing on its own; and it is accompanied by a lack of insight into one's behavior that further lessens the chances of spontaneously describing it as part of the problem (Dell'Osso et al., 2002; Youngstrom, Findling, & Calabrese, 2004). Kay Jamison has described the "seductiveness" of hypomania and mania, in which individuals not only do not feel ill, but may experience themselves as more productive, creative, or alive (Jamison, 1995). These differences result in people seeking services primarily when they are depressed, and failing to report prior episodes of hypomania or mania unless these are specifically probed. Even then, there is evidence of considerable forgetting of documented past episodes in longitudinal studies. Consequently, many cases with bipolar disorder are initially misclassified as unipolar depression. Longitudinal data often appear to indicate that the first impairing episode in bipolar disorders is a major depression (Hillegers et al., 2005; Reichart, et al., 2004), but it is not clear whether there might also be preceding hypomanic events that did not come to clinical attention.

The apparent comorbidity of depression and hypomania or mania may be exaggerated by the fact that people are more likely to seek treatment for depression and to report depression histories than they would for hypomania. Clinicians will rarely or never see cases with hypomania and no history of depression because it is not associated with distress or impairment. This is related to Berkson's bias, whereby relying only on clinical samples to study an illness biases findings about severity and correlates such as predictive powers (Berkson, 1946). Similarly, there are people with histories of repeated hypomania that never became impairing or developed into mania, and also never became depressed. This presentation is rarely seen clinically, but it occurs with some frequency in family studies of bipolar probands and also in studies of subsyndromal presentations of mood disorders, such as in college samples (Alloy, Abramson, Walshaw, Keyser, & Gerstein, 2006; Depue et al., 1981).

Section Summary

There are many methodological artifacts that could distort the apparent comorbidity between depression and other disorders, and several of these are particularly likely to be problematic with regard to mania and bipolar disorder. Given the current state of the literature, it is difficult to tell whether the net effect of these artifacts has been to underestimate the rate of co-occurrence, or to exaggerate it. Examples of both abound in the literature. Both researchers and clinicians would do well to attend to these potential confounds. Tightening up the diagnostic definitions, improving the reliability of diagnoses and consistently employing definitions of episodes and hierarchical exclusions all should increase the consistency of findings. The improved

precision would increase the statistical power to examine putative shared mechanism and allow better understanding of moderators of outcome and treatment response. It seems fair to summarize the evidence as indicating that mania and hypomania appear to involve distinct processes and can occur independently of depression, and older models positing that mania was a unitary aspect of depression, or a defense mechanism against depression do not conform well with the available data.

The relationship between bipolar disorder and major depression is more ambiguous. If the model were accurate positing that there were two independent phenomena—mania and depression—we would not expect to see such high rates of comorbidity in epidemiological settings (Caron & Rutter, 1991). Nor would we anticipate differences in the phenomenology of depression in cases with a history of bipolar versus unipolar course if these were independent but occasionally comorbid conditions.

Is Bipolar Depression Different from Unipolar Depression?

Is the depressed phase of a bipolar illness the same phenomenon as unipolar depression? If depression in both contexts is similar, then that would support a comorbidity model, where depression is one entity and hypomania or mania is a second, superimposed condition. Conversely, if there are differences in the phenomenology, etiology, pathophysiology, or course and outcome of depression associated with bipolar disorder, that would provide strong support for models of bipolar as a subtype, a distinct entity, or perhaps a phenocopy of depression.

The literature comparing bipolar depression to unipolar depression has largely concentrated on the depressed phase of people who had previously been manic (e.g., bipolar I), with a smaller number of studies looking at people with prior hypomanic episodes (e.g., bipolar II). There is an unavoidable confound based on the current nomenclature. Any sample supposedly composed of cases with unipolar depression includes people who had not yet developed hypomania or mania but who do later in life—potentially even during the course of treatment. There have been high rates of conversion to bipolar disorder documented in multiple longitudinal studies (Angst, et al., 2011; Fiedorowicz et al., 2011), and the pattern is further complicated by evidence that the mood episodes associated with bipolar disorder often onset at younger ages than cases that follow a unipolar course (Merikangas & Pato, 2009). The first episode that comes to clinical attention in bipolar disorder is often depression, too (Hillegers et al., 2005). This has led some researchers to advocate selecting more distilled groups of cases with depression, excluding those with a family history of substance use, suicide, or antisocial behavior, as well as bipolar disorder, in an effort to identify a more purely unipolar group (Drevets et al., 2002).

Genetics and Risk Factors

There is substantial overlap in the genetic factors identified for unipolar and bipolar depression. The HTTPLR serotonin transporter gene polymorphism has earned moderate support implicating it in both depression and bipolar disorder, including evidence for a gene-by-environment interaction with environmental stress (Caspi, Hariri, Holmes, Uher, & Moffitt, 2010). Evidence for this, like most genetic findings with mood disorder, is currently equivocal. With both depression and bipolar disorder, the field is moving toward models emphasizing many genes, each contributing small degrees of risk (WTCCC, 2007) and looking increasingly at epigenetic effects as important moderators of etiology and course. The genes that may convey more risk, specific to bipolar disorder, may be ones related to circadian dysregulation (Benedetti et al., 2003), although others may still be identified. Most genes of interest for depression also have some positive studies linking them to bipolar as well.

There is a similar lack of specificity in the environmental risk factors for depression and hypomania/mania. Prenatal nutrition and maternal illness, exposure to teratogens, low birth weight, family history of mental illness or substance misuse, trauma, child abuse, and stressful life events are all implicated in increased risk of both depression and bipolar disorder. Again, the hints of specificity in the literature are linked more to bipolar than unipolar depression. A family history of bipolar disorder elevates the risk of youths developing a wide variety of pathology, but the change in the odds is greater for bipolar disorder than for any other condition studied (Hodgins, Faucher, Zarac, & Ellenbogen, 2002). A few studies suggest that sexual abuse may exacerbate the risk of developing bipolar II disorder in particular (Garno, Goldberg, Ramirez, & Ritzler, 2005), but it is not clear whether this is a potent factor for a specific disorder versus a predictor of increased emotional lability and reactivity in general.

Brain Imaging and Pathophysiology

Brain imaging studies reveal a variety of similarities between bipolar disorder and depression,

including morphological changes that appear to progress with repeated episodes or longer illness duration, along with changes in functioning during cognitive and emotional tasks (Bearden, Hoffman, & Cannon, 2001; Robinson, et al., 2006). Again, more of the specific findings appear attached to bipolar disorder and not unipolar depression (Joseph, Frazier, Youngstrom, & Soares, 2008). Research in this area is complicated by the fact that it is difficult for people who are currently manic to tolerate and complete brain scans or neurocognitive testing, so much of the research has necessarily investigated trait markers of bipolar disorder rather than functioning during the manic state.

At least two related pathophysiological models also are still under active study for mood disorder in general: Dysregulation of the hypothalamic-pituitary-adreno-cortical (HPAC) axis, and chronic inflammatory cytokine activity. These systems are clearly linked, and they have an extensive body of support for depression and bipolar disorder (Raedler, 2011; Zuckerman, 1999).

Phenomenology and Associated Clinical Features

Most symptoms of depression appear similar, whether the course of illness follows a unipolar or bipolar course. Some data suggest that atypical features might be more associated with bipolar, where "atypical" refers to increased appetite, hypersomnia, and pervasive rejection sensitivity (cf. Davidson, 2007; Hantouche & Akiskal, 2005). Bipolar depression may also have significantly higher rates of psychotic features (Birmaher, Arbelaez, & Brent, 2002). Mixed mood states have been described more in bipolar disorder (Akiskal & Benazzi, 2008), but there is evidence that hypomanic symptoms may be superimposed on depression in cases that follow a more depressive course (Goodwin & Jamison, 2007; Kraepelin, 1921), leading to DSM-5 proposing a "mixed" specifier that could be used with any mood episode (American Psychiatric Association, 2012). In terms of comorbidity, the bipolar course appears more associated with panic disorder and possibly greater substance use, whereas a unipolar depressive course is associated with more generalized anxiety (Birmaher et al., 2002; Goodwin & Jamison, 2007). There is a fair degree of overlap in the distributions: most differences would constitute small or medium effect sizes.

Course

There are a variety of features that appear different with bipolar depression. The age of onset is earlier for depression with bipolar rather than unipolar course, and bipolar illness appears at higher risk to recur (Angst & Gamma, 2002). Bipolar disorder also is associated with higher risk of completed suicide, although it is unclear whether the mechanism is recurrence, poor response to antidepressants, or the great mood lability and mixed mood states associated with bipolar (Algorta et al., 2011; Berk & Dodd, 2005). Bipolar may be associated with more substance use, risk of incarceration, loss of functioning (Gore et al., 2011; Lopez, Mathers, Ezzati, Jamison, & Murray, 2006), and adverse medical outcomes (Goldstein, Kemp, Soczynska, & McIntyre, 2009). Intriguingly, these may not be attributable to the mania and even less likely to the hypomania. These mood episodes have nonadditive effects and may even buffer against some of the adversity in depressive episodes (Freeman et al., 2009; Johnson et al., 2012). This draws more interest to the unique characteristics of bipolar depression that contribute to greater impairment.

On balance, it seems that bipolar disorder is associated with a moderately greater burden of illness than unipolar depression. Simple additive models of comorbidity would predict an increment in impairment. Having two conditions at the same time would often generate more impairment than either alone. However, the studies examining incremental effects of hypomanic and manic symptoms have not found evidence of additive burden, and even found suggestion of buffering instead. These cross-sectional findings are superficially inconsistent with the greater burden of bipolar illness longitudinally. It is possible that some of the adverse outcomes are due to recurrence, and others may be iatrogenic effects of treatment, as many of the anticonvulsant and antipsychotic medications are associated with substantial weight gain, which is much less of an issue with antidepressants (Correll, 2008). However, other work links mood disorder to obesity and inflammation independent of medication effects (Goldstein et al., 2009). The overall pattern of findings is clearly inconsistent with a single entity underlying both mania and depression, and also does not square well with a simple, additive comorbidity model. Instead, it seems most reconcilable with either a subtypes model (i.e., bipolar depression as an entity that might share some processes with other forms of depression, but also has distinct features), a "modifiers" model, or bipolar as a distinct entity. For a dimensional model, the differences in course would require invoking either a moderator hypothesis, in which the hypomanic/

manic episodes modify the course of the mood episodes, or else thinking in terms of equifinality, where different mechanisms and processes lead to what appears to be a shared outcome (Cicchetti, 2010).

Treatment Response

Mania and depression show distinct responses to different compounds. Few drugs have demonstrated both antidepressant and antimanic efficacy, and none appear equally potent in acute treatment of both poles of mood problems (Yatham et al., 2005). Pharmacological treatment studies suggest that bipolar depression responds differently than unipolar depression to many compounds. Most industry-sponsored studies for antidepressant medications now exclude people with a history of hypomania or a family history of bipolar disorder as a result.

More subtly, there are differences in treatment response within depression. A variety of agents with established efficacy for treatment of depression have no effect on mania. There is considerable debate about whether antidepressants trigger hypomania or mania in people with a bipolar diathesis. Two reviews recently concluded that the most likely interpretation is that antidepressant use is associated with greater vigilance for potential subsequent hypomanic symptoms, leading to differential rates of detection, but not actual increases in incidence based on blinded trials (Joseph, Youngstrom, & Soares, 2009; Licht, Gijsman, Nolen, & Angst, 2008). Recent large studies also find no evidence of increased switch to hypomania or maniabut, unfortunately, also find no evidence of therapeutic benefit on average for using antidepressants to treat bipolar depression (Perlis et al., 2006). Less research has investigated the use of anticonvulsants or atypical antipsychotics for the treatment of unipolar depression, because the greater potential burden of side effects tips the scales against using them as first-line treatments for depression.

Psychotherapy research has concentrated more on the treatment of unipolar depression. Most psychotherapies studied with bipolar disorder are investigated as adjunctive treatments used in combination with pharmacotherapy. Cognitive-behavioral-therapy techniques developed with unipolar depression have not demonstrated large treatment effects in bipolar disorder (Lam, 2002; Scott & Colom, 2005), and proponents have made a variety of modifications to the protocols to address features that are more prominent or specific to bipolar disorder. These include emphasizing sleep hygiene, focusing on emotion regulation and balance instead of increased activation, developing behavioral management strategies to address hypomania, and addressing dysfunctional positive automatic thoughts as well as negative ones (Feeny, Danielson, Schwartz, Youngstrom, & Findling, 2006; Frank, 2005; Newman, Leahy, Beck, Reilly-Harrington, & Gyulai, 2002).

Overall, the treatment literature clearly refutes the model that mania and depression are a single illness. The data again are more consistent with models positing that unipolar depression and bipolar disorder are subtypes or distinct entities, perhaps with some shared processes or endpoints. Alternately, it might make sense to conceptualize hypomania or mania as a treatment modifier, altering the choice of interventions and changing the content of psychotherapy.

Clinical Implications when Working with Depression

The unipolar/bipolar distinction definitely has clinical utility. Identifying that a person seeking treatment for depression has a bipolar spectrum version of illness predicts a different course of illness, changes the risk of key clinical sequelae, prescribes a different choice of initial treatment, and modifies the process of working with the patient over time. Although lagging behind advances in the treatment of unipolar depression, there is a growing body of literature around treatments for bipolar disorder.

The Food and Drug Administration has suggested that anyone taking an antidepressant medication or prescribing one for depression should perform "due diligence" about assessing for history of hypomania or mania, as well as family history of bipolar disorder. Some experts advocate using a dimensional approach to case conceptualization, such as using an "index of suspicion" for potential bipolarity to integrate the different risk factors and clinical features that might alter the diagnosis or treatment (Phelps, Angst, Katzow, & Sadler, 2008; Sachs, 2004). A dimensional framework also lends itself to more Bayesian approaches to interpreting assessment findings, and evidence-based medicine offers a framework for translating these probabilities into decisions about the next clinical action (Guyatt & Rennie, 2002). Recent work has explored ways of synthesizing rating scales, family history, and findings about other risk factors into a fast and frugal yet evidence-based approach to improving the differentiation of unipolar and bipolar mood disorder in clinical practice (Youngstrom, et al., 2009).

Practitioners can immediately improve their clinical decisions by systematically assessing for history of hypomania or mania whenever working with depression, recognizing other risk factors that may be increasing the probability of a bipolar course, and teaching the patient to monitor mood and energy changes prospectively as a way of identifying hypomania, mixed presentations, and incipient mania. Better characterization of the risk of bipolarity allows for more titrated treatment choices, balancing the risks against potential benefits more accurately.

Agenda for Future Research

Taxometric studies are not indicating clear boundaries between unipolar and bipolar mood conditions. Similarly, the evidence for mixed presentations requires more careful measurement. Applying categories has created research samples containing mixtures of different conditions. Categorical approaches have also contributed to poor measurement, by assuming that unipolar depressed samples have no hypomanic features, and so forth. Much of the research literature based on putatively unipolar depressive samples actually includes blends of unipolar depression, bipolar II, and "latent" bipolar that has not yet manifested a hypomanic or manic index episode. The poor stability of retrospective recall of hypomania and the poor reliability of bipolar diagnoses also contribute to the failure to identify bipolar cases. All these methodological factors attenuate the effect sizes of results. It also would be helpful for research to use multiple informants and information sources, even in work with adults. Collateral informants provide a different perspective on irritability (Bartels, et al., 2004), and often a more valid perspective on hypomania and mania (Youngstrom, Findling, & Calabrese, 2004). A simple step forward would be to include a brief measure of hypomanic or manic symptoms in studies working with depression, to quantify the degree of "mixed" presentation. Systematically gathering past history of hypomanic or manic symptoms also would advance understanding about the role of bipolar features as a moderator of course or outcome.

When it is necessary to use mood categories in research, it would be helpful to focus more on observed mood episodes and less on diagnostic category—unless the study is using an event history model that explicitly models cases with no history of mania as "right censored." Given the nature of the illness, we are more certain about the diagnostic status of cases in which we have documented hypomania or mania. In contrast, all we can say about others is that they have not developed a mania or hypomania yet; the "right censoring" weights these cases differently, acknowledging that it is possible that they will develop bipolar features in the future. More investigations of depression may want to adopt an event-history approach, modeling time to onset or recurrence, and using hypomanic/manic features as a predictor (or including hypomanic, manic, or mixed episode as a distinct endpoint in survival analysis).

It will be important to characterize the onset, duration, chronicity, and recurrence of episodes. A failing of the current nosological systems is that they have de-emphasized the focus on course, potentially missing one of the aspects of presentation that could be most helpful in classification and treatment selection (Klein, 2008). Rapid relapse would be another clinically important marker that has not been well studied yet (Dunner, Patrick, & Fieve, 1977). Focusing on distinct episodes will help clarify the distinction of mood disorders versus other conditions (Leibenluft, 2011; Youngstrom, 2009). It also is intrinsically less complicated than assembling diagnoses, and it is closer to the observable phenomenon. A simplified way of measuring might be to ask about manic and depressed symptoms currently, and in the worst past episode. This creates a set of four variables. The key hypothesis would be to test whether worst lifetime hypomania/mania level moderates other variables (both proximal and distal). An alternative would be creating groups based on presence/absence of hypomania/mania or depression, looking at both current functioning and worst past; however, this would imply 16 cells ($2 \times 2 \times 2 \times 2$), creating power problems.

Future research also would profit from dismantling syndromes concentrating on particular symptom clusters, such as circadian dysregulation or appetite disturbance, and examine underlying mechanisms. These more narrowly defined constructs are likely to be easier to link to underlying processes, consistent with the concept of "endophenotypes" (Hasler, Drevets, Gould, Gottesman, & Manji, 2006). The research-domain-criteria (RDoC) approach advocated by the National Institute of Mental Health is congruent with this reconceptualization of research as focusing on specific mechanisms rather than global diagnoses (Cuthbert, 2005). We hypothesize that these approaches will identify some processes that are shared between bipolar disorder, unipolar depression, and other

psychopathology, as well as identifying more focal mechanisms that may be specific to only subsets of cases within mania or depression.

General Conclusions

The body of evidence accumulated over the past century strongly refutes the model that mania and depression are simply different expressions of the same underlying psychic process or illness. The data also are not consistent with a simple, additive model of comorbidity that treats depression and mania as independent conditions that occasionally co-occur. Present information does not decisively indicate a winner from among contending models that describe unipolar depression and bipolar disorder as subtypes of mood disorder, versus bipolar features as being a moderating variable changing course and outcome, or distinct illnesses with some shared features in endpoints—the "equifinality" or "phenocopy" models. Our hypothesis, which remains to be tested against future data, is that the broad category of mood disorders will prove to contain several entities that share some common diatheses and processes, but also involve some distinct components that distinguish between bipolar versus typical unipolar depressive trajectories. For the moment, it is valuable for clinicians and researchers to be aware of the potential for bipolar "comorbidity" whenever working with depression. Regardless of whether hypomania and mania prove to be a "true" comorbidity, a subtype of mood disorder, or a distinct but often misconstrued entity, the failure to systematically assess the bipolar aspects of mood functioning has hindered research and compromises clinical care.

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CHAPTER

18 Depression and Cardiovascular Diseases

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Abstract

This chapter provides a selective review of empirical studies concerning the relationship between depression and depressive symptomatology as risk factors for cardiovascular diseases. Depression appears to confer a twofold risk for both cardiac disease incidence and cardiac disease progression. Several factors appear to contribute to this risk, including the effects of depression on immune activity, endothelial function, SNS and HPA activity, and medical adherence. However, it remains unclear whether depression is only marking risk of some unmeasured third variable responsible for increased heart disease. Although antidepressant medication and cognitive behavioral therapy produce some reduction of depression in cardiac patients, there are no definitive clinical trial data showing medical or behavioral treatment reduce cardiac deaths. Only large-scale randomized clinical trials can fill this gap. The chapter concludes with a series of critical questions requiring resolution to decide what treatment would work most effectively for the cardiac patient with depression.

Key Words: depression, cardiac disease, cardiovascular diseases

An age-old question is whether affective disorders confer risk for physical disease, with depression and cardiovascular diseases (CVD) often being the favored candidates. In the last three decades, appreciable advances have been made in epidemiology, medicine, psychiatry, and clinical behavioral medicine to understand how affect contributes to cardiac diseases. By *cardiovascular diseases*, we mean the inability of the coronary circulation to supply adequate blood to cardiac muscle and surrounding tissue. The best-known disorder is coronary artery disease (CAD; also more commonly called coronary heart disease [CHD]), which is caused by the accumulation of plaque within the walls of the arteries that supply the heart muscle. Angina pectoris, which is chest pain, and myocardial infarction (known commonly as heart attack) are symptoms of and conditions caused by CHD. Another condition is cardiomyopathy, which refers to the deterioration of the function of the heart muscle. Myocardial infarction or cardiomyopathy may lead to congestive heart failure (CHF), the inability of the heart to supply sufficient blood flow to meet the needs of the body. People with cardiomyopathy are often at risk of arrhythmia and/or sudden cardiac death.

Since the last century, CVD is the single most prevalent cause of death in men and women. Approximately 80 million Americans have CHD, which is associated with $475 billion of direct and indirect costs (AHA, 2010). Identifying factors that confer high risk, promoting healthy practices, and developing effective interventions to stem this lethal condition have been high priorities for the community of scientists and practitioners.

Epidemiological research has documented risk factors for CHD, including unhealthy ratios of

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low-density lipoprotein (LDL, "bad cholesterol") and high-density lipoprotein (HDL, "good cholesterol"), elevated blood glucose levels, high blood pressure, smoking, and obesity. These are considered as traditional or conventional cardiac risk factors. The pursuit of biological risk factors has continued because even the best combination of traditional risk factors only modestly predicts new cardiac cases (Mokdad, Marks, Stroup, & Gerberding, 2004; but see Greenland et al., 2003). Recent candidates, still under active study, are C-reactive protein, an index of inflammation (Ridker et al., 2005) and various genomic profiles.

The idea that psychological factors also confer cardiac risk is as old as Galen and Hippocrates' speculations about certain emotional dispositions leading to physical illness. Skipping to the first half of the 20th century, psychiatrists offered proposals inspired by Freudian thinking. Only the introduction of modern epidemiological methods, however, allowed claims to be tested with empirical evidence. In the 1970s, the most prominent candidate was Type A, a behavioral complex consisting of achievement-striving, irritation, time urgency, and anger (Friedman & Rosenman, 1974). However, as negative evidence accumulated, anger/hostility—a subcomponent of Type A—emerged as the actual toxic agent (Matthews, Glass, Rosenman & Bortner et al., 1977; Smith, 1992). In the late 1980s and 1990s, a second candidate emerged from case-control and prospective studies: depression and elevated depressive symptoms (Carney et al., 1988). Since then, mounting evidence continues to support the connection between depression and heart disease (Meijer et al., 2011; Van der Kooy et al., 2007).

In this chapter, we will selectively review the epidemiological literature for the association between depression and CHD, the most commonly studied of the CVDs. We then will consider mechanisms of action and describe the complex, reciprocal relationships between depression and CHD. In the next-to-last section, the effects of pharmacological and behavioral treatment for depression to reduce cardiac risk will be summarized. In the final section, we will consider some persistent questions and challenges for research, practice, and future directions.

Epidemiology of Depression and CHD

Whereas, depression is seen in 4 to 7% of the general population (e.g., Ariyo et al., 2000), it ranges from 14 to 47% in CHD patients (Carney et al., 1988; Frasure-Smith, Lesperance, & Talajic, 1993; Schleifer et al., 1989). When DSM criteria are used to establish a diagnosis, prevalence tends to be somewhat lower (i.e., 15–20%), but even minor depression or elevated depressive symptoms are seen in 20–30% of CHD patients (Frasure-Smith et al., 1993). Importantly, both clinically diagnosed depression and elevated depressive symptoms predict increased cardiac risk. Such evidence lends credibility to the idea that depression contributes to development of heart disease, but because many of these studies contained cross-sectional analyses, direction of causation is ambiguous.

Prospective studies of nominally healthy populations (at baseline) have helped to clarify the role of depression on initiation (as opposed to progression or recurrence) of heart disease. Although there are some null findings, the majority of studies following persons without CHD (at baseline) find depressed individuals (usually operationalized with a self-report inventory about depressed symptoms, such as the Beck Depression Inventory; Beck, Ward, Mendelson, M., Mock, J., & Erbaugh, 1961 or the Center for Epidemiological Studies—Depression subscale; Radloff, 1977) have about a twofold increase in relative risk of development of CHD, after adjusting for traditional risk factors, compared to those with low symptom scores (Wulsin & Singal, 2003). Several studies also have followed CHD patients, who were evaluated for depression with clinical interviews or questionnaires, to assess future cardiac events and/or mortality. Some studies only recruited those with stable CHD, others focused on patients hospitalized for acute myocardial infarction, congestive heart failure, or coronary bypass surgery. Again, although there are exceptions, in the majority of studies, depression during or shortly after hospitalization was associated with a two- to threefold risk for mortality or nonfatal cardiac events (e.g., Carney & Freedland, 2008). A final, important point is that a comparison of results for studies with healthy samples at baseline versus studies of populations with known CHD indicates that the predictive association between depression/depressive symptoms and subsequent cardiac events and mortality (adjusting for traditional risk factors) is more robust and reliable among those who already have cardiac disease (e.g., Suls & Bunde, 2005). Perhaps for this reason, patients with existing CHD have been the predominate targets of research.

Biological and Behavioral Processes Linking Depression and Cardiac Disease

Several nonmutually exclusive mechanisms have been implicated in the association between cardiac disease and depression (see Everson-Rose, & Lewis, 2005; Suls & Bunde, 2005 for reviews).

Platelet Activity

Platelets are cells that circulate in the blood; if they aggregate in large numbers they create clots that can block blood flow, thereby playing an important role in causing a myocardial infarction. Results show that depressed patients have greater platelet aggregation (Musselman et al., 1996). Interestingly, SSRIs have antiplatelet properties in humans and can inhibit platelet aggregation (Shimbo et al., 2002). This has been the rationale for using sertraline, an SSRI, to produce better cardiac outcomes, possibly through platelet aggregation reduction (see later).

Inflammation

Cytokines are protein molecules secreted by cells and serve as modulators of immune-system activation. Relevant to this chapter, proinflammatory cytokines play a prominent role in the formation of atherosclerotic plaque, its progression and rupture, thereby directly contributing to CHD. Epidemiological studies also have found that proinflammatory cytokines, such as interleukin-6 and C-reactive protein, are independent predictors of CHD mortality (Kop, et al., 2010). Elevated levels of cytokines also are associated with depression in patients with and without a history of cardiac disease (Howren, Lamkin, & Suls, 2009; Miller, Maletic, & Raison, 2009; Pizzi et al., 2009;). This raises the possibility that inflammation associated with depression predicts subsequent cardiac events. Indeed Vaccarino et al. (2007) reported that depression predicted ischemic events, but the association was significantly reduced (but not eliminated) when CRP and IL-6 were entered as predictors.

Endothelial function

In its normal state, the endothelium (inner lining of blood vessels) facilitates vasoconstriction and vasodilation of the vessels. However, when the endothelium does not release nitrous oxide (NO), vasoconstriction follows, which can facilitate coronary thrombosis, or vessel blockages. Interestingly, inflammation impairs NO release (Hingorani et al., 2000). Meanwhile, persons with depression or elevated depressive symptoms tend to show endothelial dysfunction (Sherwood et al., 2005). Researchers (Pizzi et al., 2009) have found patients treated with SSRIs show improved endothelial function.

HPA Axis

Depressed persons tend to exhibit high baseline cortisol (e.g., Akil et al., 1993). In addition, cortisol is not suppressed after dexamethasone administration in depressed patients (Ehlert, Gabb, & Heinrichs, 2001). Some researchers emphasize the *variability* in hypothalamic–pituitary–adrenal (HPA) axis activity—where cortisol is secreted from—rather than high levels of its secretions is the culprit system that is dysregulated in those with depression (Pariate & Lightman, 2008). Such dysregulation is associated with several cardiac risk factors, such as increased blood pressure and heart rate, obesity, and elevated cholesterol and triglycerides (e.g., Rosmond & Bjorntorp, 2000).

Autonomic Dysregulation

One consequence of a dysregulated autonomic nervous system is reduced heart-rate variability (HRV), which represents the variability in the beat-to-beat interval. Heart-rate variability is a function of sympathetic and the parasympathetic nervous system inputs and neurohumoral factors. Reduced HRV reflects the inability of the body to efficiently respond to different energy demands. Several studies show that depressed persons tend to exhibit reduced HRV (Carney & Freedland, 2009). In addition, reduced HRV is associated with increased incidence of cardiac events (Bigger et al., 1992) so there appears to be a connection between depression, HRV, and cardiac outcomes.

Behavioral Factors

Besides these physiologic mechanisms, behavioral factors also may play a significant role. Depression is associated with a less healthy diet, sedentary behavior, and smoking (Whooley et al., 2008; Ziegelstein et al., 2000). All these behavioral risks confer increased risk of cardiac disease in persons without CHD and in the nominally (physically) healthy. Depressed persons also adhere more poorly to medication and exercise recommendations (May et al., 2010; Ziegelstein et al., 2000). After depression has improved, medication adherence (e.g., aspirin) increases; but for patients whose depressive symptoms increase, adherence becomes poorer. Changes in adherence, however, are unrelated to subsequent changes in depressive symptoms (Rieckmann et al., 2006)

A Central Place for Cytokines?

From the preceding discussion, it is clear that pathophysiology and behaviors independently and in interaction may explain the connection between depression and cardiac disease. Most of these processes imply that depression predisposes the development of CHD. However, there is actually

a plausible basis for bidirectional causation with inflammation, or the pro-inflammatory cytokines (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008), playing an important meditational role.

Experimental research with animal models demonstrates that cytokines induce a "sickness behavior" complex, characterized by withdrawal from the physical and social environment that is accompanied by pain, malaise, and decreased reactivity to reward (anhedonia). Depression shares many features with sickness behavior. Moreover, major depressive disorders develop in roughly a third of patients who are treated with the recombinant human cytokines IL-2 and interferon-α (IFN-α) (Asnis & de la Garza, 2006). Depression is also more prevalent in patients with conditions that lead to chronic inflammation (such as cardiovascular diseases).

Sickness behavior should not be equated with depression (Dantzer et al., 2008) because the former is an adaptive response to infection by pathogens and fully reversible once the pathogen has been cleared; this is not the case for depression. However, persons with a high inflammatory profile are likely to have high HPA axis activity, autonomic imbalance, and high serum serotonin levels, all of which contribute to cardiopathogenesis. In addition, inflammation, particularly macrophages and pro-inflammatory cytokines, play a direct role in atherosclerosis (Danesh et al., 2004; Kop & Gottdiener, 2005; Ross, 1999). These considerations provide credence to the view that an underlying inflammation creates a cascade that increases both the development of depression and cardiac disease.

A recent test of this hypothesis in humans did not reveal that increased peripheral cytokines (assessed via C-reactive protein) preceded depressive symptoms; however, because baseline depressive symptom severity increased, there was a significantly lesser decrease in 1-month CRP (Shaffer et al., 2011. This still leaves open the possibility that some persons are vulnerable to "sickness behavior" syndrome when exposed to a high cytokine load, but this "rare" phenotype hypothesis has yet to be tested. It is also possible that central (as opposed to peripheral) cytokines are responsible for the increased depression, as well as the increased risk of CHD. However, invasive measures of central or brain cytokines remain only possible in animal models.

This focus may seem to give too little significance to the role of life stressors and cognitive errors contributing to depression and later cardiovascular pathogenesis. However, the sickness behavior perspective does not rule out the equally plausible scenario that stressful life events and the challenges of everyday life can produce SNS and HPA axis dysregulation, thereby disrupting the glucocorticoid feedback system and producing exaggerated immune activation, that in turn contributes to atherogenesis and eventual frank cardiovascular disease (Lovallo, 2005).

Summary

Although there is evidence for several pathogenic processes and behavioral factors contributing to the association between CHD and depression, researchers have not moved much beyond a laundry list of plausible candidate mechanisms. Inflammatory processes may prove to play a central role, but it would be premature to draw any conclusions at this stage, and recent tests of this interesting hypothesis have proved disappointing.

Interventions with Cardiac Patients

Because depression appears to place cardiac patients at increased risk for recurrent MI or premature mortality, clinical health psychologists and psychiatrists have considered the possibility that treating depression will reduce cardiac risk. The most common treatments for depression are psychotherapy and antidepressant medication (Olfson & Marcus, 2009).

Antidepressant Effects

Currently, serotonin reuptake inhibitors, such as fluoxetine, paroxetine, fluvoxamine, citalopram and sertraline, are the drugs of choice for treating depression in the general population (Kirsch et al., 2008). Another class of drugs, tricyclics, may sometimes be prescribed to treat depression, but are not recommended to cardiac patients because tricyclics can affect heart rate and rhythm (Glassman & Bigger, 1981). There is some consensus that antidepressants are appropriate for cases of moderate to severe depression, but psychotherapy may be better for mild depression because medication does not seem to be effective in those cases (Moncrieff & Kirsch, 2005).

With respect to CHD patients, two questions about the effects of antidepressants are relevant: First, are they a safe and effective way to treat depression in the context of cardiac disease? Second, do antidepressants reduce the subsequent recurrence of cardiac events? In regard to the first question, we know that persons with general medical conditions who also have depression, can be treated safely and effectively with SSRIs with no adverse effects or tolerability burden, relative to their counterparts without such

conditions (Morris et al., 2012). Evidence for combined serotonin-norepinephrine reuptake inhibitors is still unclear (Celano & Huffman, 2011).

Turing to cardiac patients, there have been six major SSRI trials published to date. In all of these, antidepressants appeared to be safe and caused no risk of adverse events. In four of the trials, there was evidence of mild improvement, based on Hamilton scores or comparable indices. However, significant differences with placebo controls were not always obtained.

The efficacy of antidepressants in reducing cardiac risk is less clear. The SADHART study found lower rates of combined cardiac events associated with sertraline administration (vs. placebo), but the difference was non-significant (Glassman et al., 2002). SADHART, however, was not powered to test for a difference in cardiac events. Also relevant is the Enhancing Recovery in Coronary Heart Disease (ENRICHD) trial that was conducted to test the efficacy of cognitive behavior therapy (CBT; see later) in post-MI patients with minor or major depression (Writing Committee for the ENRICHD Investigators, 2003)) If patients did not respond to the CBT after 5 weeks or if their depression was severe at the outset, they could start antidepressant medication (usual care patients also could receive medication from their physician). At the 6-month follow-up, patients taking antidepressants had significantly lower rates of death and recurrent MI versus patients not taking antidepressants.

These empirical trends are encouraging about the benefits of antidepressants for cardiac patients. However, SADHART had limited statistical power, and ENRICHD lacked blinding and antidepressant medication was not randomly assigned. Four other antidepressant trials with cardiac samples did not find decreases in cardiac risk or mortality, but they, too, were unpowered. A large Finnish population study of over 15,000 reported antidepressant users showed a lower risk of CHD and stroke mortality risk versus no depressant use (Tiihonen et al., 2006). However, the sample was restricted to patients with history of a suicide attempt. And, in 63,000 women followed in the Nurse's Health Study, antidepressant use predicted sudden cardiac death (Whang et al., 2009), suggesting that a properly powered trial is required to properly answer this question.

Psychological Treatment of Depressed CHD patients

Several types of short-term behavioral treatment, such as cognitive therapy, cognitive behavior modification and interpersonal therapy, have been successful in treating depression (see Ebmeier, Donaghey, & Steele, 2006; Kupfer, Frank, & Phillips, 2012). Cognitive therapy, based on Beck, Rush, Shaw, & Emery's (1987) approach, systematically attempts to correct the patient's cognitive errors or biases contributing to depression. Interpersonal therapy targets depressive symptoms, interpersonal relationships and self-esteem (Elkin et al., 1989). Cognitive behavior therapy provides insight and skills to recognize how thoughts, feelings, and behaviors can cause depression.

There also has been considerable testing of psychological interventions, such as stress reduction, individual and group psychotherapy, in the general cardiac population (i.e., not targeting the depressed subset of patients). The general goal of these treatments is to reduce patient distress leading to improvements in clinical outcomes, such as mortality, morbidity, and quality of life (for a review see Linden, Phillips, & Leclerc, 2007). To illustrate, one intervention trial recruited men who recently experienced an MI who were randomly assigned to usual care or a psychosocial intervention involving monthly phone monitoring by a nurse. One year later, patients who received the intervention were less distressed and had less mortality (Frasure-Smith & Prince, 1985). In other studies with CHD patients, comparable benefits of stress management and CBT have been found (e.g., Blumenthal, et al., 2002). Although the majority of studies show positive effects, there have been some conspicuous exceptions. For example, another trial comparing phone monitoring versus usual care recruited CHD patients reporting high levels of distress. No changes in anxiety or depression symptoms were found at 1-year follow-up or in recurrent MI or cardiac death, and there was a tendency to have increased deaths in a subgroup of women receiving the stress monitoring (Frasure-Smith, et al., 1997).

Behavioral Interventions with Depressed Cardiac Patients

To date, there are three randomized clinical trials reporting the effects of psychological treatment, typically in combination with antidepressants, in depressed cardiac patients. The largest was the multisite ENRICHD, which was already mentioned (Writing Committee for the ENRICHD Investigators, 2003)). It recruited approximately 2,500 post-MI patients who were diagnosed with depression using a clinical interview (an independent entry criteria was low social support). Patients

were randomly assigned to usual care or CBT for six months. Cognitive behavior therapy was associated with greater decreases in depression severity versus usual care, but the latter also showed improvement. As this trial was statistically powered to detect a difference in deaths, it was disappointing the conditions did not differ in rates of recurrent nonfatal MI (approximately 14%), cardiac death (8%) or all-cause mortality (14%). Several subsidiary analyses have been published to consider the effects of various moderator variables. As noted earlier, those who additionally received antidepressants seem to have a cardiovascular benefit in this trial, but when patients were split into four groups (minority men, minority women, white men and white women) it again appeared as though there was a trend to harm for the minority women, when receiving treatment (Schneiderman et al., 2004). It is important to note that subgroup analyses of this type from a randomized trial, even if large, should be considered as hypothesis-generating, and never as confirming, since randomization is not preserved in these exploratory analyses.

The Coronary Psychosocial Evaluation Studies (COPES; Davidson et al., 2010) involved a 6-month enhanced-care intervention comprised of problem-solving therapy or antidepressant medication, depending on patients' preferences, with the option of later augmentation with the other treatment, intensification of the intervention or treatment switching. Both depressive symptoms and major cardiac events were reduced versus the usual care arm of the trial. The implication is that patient preference and stepped-care may be a beneficial combination.

Collaborative care programs for depressed medical patients involve a nurse or social worker, who interacts with the patient, a consulting psychiatrist and primary medical care provider to coordinate the patient's treatment among providers (e.g., Katon et al., 2004). In the "Bypassing the Blues" trial, Rollman et al. (2009) tested the effects of collaborative care, delivered on the telephone to a sample of depressed patients following coronary bypass surgery whereas the controls were assigned to usual care. After 8 months, the treatment group showed a greater reduction in depressive symptoms and more improvement in quality of life than usual care patients, but rehospitalizations for cardiac causes did not differ between treatment and controls (both 32%). There were clear trends for men to benefit more from collaborative care than did women.

A third trial also focused on depressed patients who underwent CABG (Freedland et al., 2009), but compared the efficacy of CBT, or supportive stress management, to usual care. Both of the active treatments were associated with greater reduction of depressive symptoms than usual care at 3 months, however only CBT maintained these benefits 6 months later. The sample was too small to be able to detect differences in cardiac mortality.

Although the findings of these trials are encouraging, only ENRICHD had the statistical power to adequately detect differences in cardiac mortality. As discussed later, researchers need to pursue several lines of investigation to assess the value and the feasibility of making behavioral treatment for depressed cardiac patients part of clinical guidelines.

Beneficial Effects of Exercise

A different treatment approach has been proposed by Blumenthal, who noted that exercise has positive benefits for many of the mechanisms assumed to be responsible for the connection between cardiac disease and depression. For example, aerobic exercise can reduce HPA axis arousal (Wittert, Livesey, Espiner, & Donald, 1996), autonomic dysregulation (Claytor, 1991), and inflammation (Ford, 2002). Moreover, exercise is strongly recommended in cardiac rehabilitation (Lawlor & Hopker, 2001).

An early study, including a usual-care arm (Stern, Gorman, & Kaslow, 1983), found that male cardiac patients with elevated depression who had been randomly assigned to 12-weeks of structured exercise had fewer cardiovascular-related sequelae, such as strokes or recurrent MI. No differences emerged for cardiac deaths, which is not surprising as the sample comprised only about 100 patients.

In one of the best-known recent studies, depressed older adults were assigned to exercise, antidepressant medication or both (Blumenthal et al., 1999). Exercise was as effective as antidepressant medication in reducing depression by the conclusion of the 16-week program. Further, those who continued to exercise were less likely to show relapse at 10-month follow-up (Babyak et al., 2000). The design was limited by absence of a placebo control comparison. In a replication trial that did have a control arm, exercise improved markers of cardiac risk, but was not powered to detect differences in cardiovascular outcomes (Blumenthal et al., 2005). This latest trial also demonstrated that stress management also showed the same improvements, compared to usual care.

Summary

Most reviews of this literature (Celano & Huffman, 2011; Lett et al., 2004) conclude that despite the availability of effective treatments for depression, there is still too little evidence to support the efficacy of these treatments for depressed cardiac patients. Nonetheless, the existing evidence and the accumulated knowledge about the mechanisms underlying depression and heart disease support the continued pursuit of these issues.

Persistent Questions Plaguing the Field of Depression and Heart Disease

Although enormous strides have been made in understanding and exploring the association between depression and heart disease, five scientific puzzles remain that require continued investigation. Each will be presented, along with suggestions for future research needed to answer these questions in the near future.

Is It Depression qua Depression That Is a Risk Marker for CHD?

Despite the multitude of prospective, observational studies that have documented a prospective, independent association between depression and incidence or recurrence of frank or overt CHD, doubt remains about whether we have sufficient data to presume that it is depression itself that precedes CHD, or if it is instead a cardiovascular disease process underlying the eventual manifestation of a myocardial infarction that is also causing elevated depressive symptoms. This is sometimes called reverse causality, because the researcher mistakenly identifies variable A as likely implicated causally in the manifest version of variable B, whereas, in reality, the latent (or silent, or subclinical) version of variable B is really causing variable A. A promising direction that some investigators have begun to explore is the more extensive use of cross-lagged panel observational designs to address this issue. For example, subclinical atherosclerosis (a latent version of CHD) (Goodman, Shimbo, Haas, Davidson, & Rieckmann, 2008) directly leads to a manifest or frank CHD. Cross-lagged panel models can examine the predictive association between two variables over time, each controlling for effects at earlier time points. Although they remain observational, they can rule out reverse causality, that is, that worsening CHD processes, for example, actually precede increased depressive symptoms, rather than the reverse.

Another reason why depression is still considered only tentatively a CHD risk marker is because research may not have considered all possible medical or other unmeasured variables that could instead be responsible for the empirical association between the two. Thus, there continues to be a concern that a third common variable, such as the presence of renal disease (Boulware et al. 2006) or the severity of heart failure (Nicholson, Kuper, & Hemingway, 2006), are causing both the depressive symptoms and the occurrence of frank CHD. Unmeasured third common causes can be investigated in future observational studies by including assessments of the hypothesized third causal variable. Indeed, many observational studies have started including global CHD risk scores, and other such measures, to ensure that it is not merely some other common disease that is, in fact, causing both the depression and the cardiovascular event (Kronish, Rieckmann, Schwartz, Schwartz, & Davidson, 2009). However, ever-increasing inclusion of medical, psychiatric, sociodemographic, and other potential common explanatory variables will never fully quell this concern. The cross-lagged models, while promising for exploring a reverse-causality problem, rarely address spuriousness by controlling for third common variables. Thus, this remains a persistent question about the research area of depression and heart disease, at least as long as we continue to use observational designs to address this issue. In summary, is it really depression itself that is marking risk for increased heart disease? Observational studies can never fully rule out alternative explanations for the repeatedly found association.

What Is the Role of Depression's Overlap with Other Negative Affective Risk Factors?

Depressive disorder and depressive symptoms have distinct features, but they also have many symptoms that overlap with anxiety and anger/hostility, two other presumed risk factors for cardiac disease (Kubzansky & Kawachi, 2000; Roest, Martens, de Jonge, & Denollet, 2010; Smith, 1992). Self-report measures of depression and anxiety are strongly associated (r's between .4 & .8) (Watson et al., 1995) and there are also high comorbidity rates (50–60%) between anxiety and depressive disorders (Mineka, Watson & Clark, 1998). The association of depression with anger/hostility has been less extensively assessed with self-report measures, but available studies show associations tend to be in the 0.50 range (Costa & McCrae, 1992; Friedman & Booth-Kewley, 1987).

Such associations, besides representing measurement overlap among the three affective dispositions, also suggest that there may be construct overlap as they share negative affect at the core of each respective definition. Further, several of the physiologic processes thought to underlie depression's connection to cardiopathogenesis also apply to anger/hostility and anxiety. Measurement, construct, and mechanism overlap pose a problem for interpretation of epidemiological studies reporting that depression or depressive symptoms predict cardiac mortality: Is it depression per se, the other negative affects, their shared core, or even their combination that confers cardiac risk? Suls and Bunde (2005) found a few studies that have compared the three affective dispositions' independent and combined effects for prediction of cardiac outcomes. And, since 2005, a small set of epidemiological studies and secondary analyses have been published (e.g., Kubzansky, Koenen, Jones, & Eaton, 2009; Smoller et al., 2009), which have attempted to address this interpretational problem. The majority of these studies find that depression predicts cardiac outcomes independent of anxiety, but no definitive conclusions can yet be drawn from this small set of studies. Beyond the conceptual and mechanism problems created by the overlap among these three negative affects, it also begs the question about whether successful targeting and treatment of depression would be sufficient to reduce cardiac risk or whether problems with anger and anxiety also need to be addressed, if cardiovascular outcomes are to be improved.

What Type of Depression Is a Risk Marker for CHD?

If we leave aside for a moment the question of whether it is truly depression that is associated with CHD, another vexing question for the field is what type of depression, or type of depressive symptom cluster, is actually associated with later CHD. Major depressive disorder (MDD) is a clinical syndrome defined by the presence of at least five of nine symptoms, for at least two weeks. The nine symptoms include: disrupted appetite (with accompanying weight change); disrupted sleep; psychomotor agitation or retardation; fatigue and reduced energy; feelings of worthlessness or inappropriate guilt; indecisiveness and diminished concentration; recurrent thoughts of death and/or suicidal ideation; depressed mood; and loss of interest or pleasure (anhedonia). For a diagnosis of MDD, depressed mood and/or anhedonia must be present (American Psychiatric Association, 2000). Thus, depression is clearly a multifactorial clinical entity, or a complex phenotype. Many studies have now attempted to assess the association of isolated symptoms or symptom dimensions of depression with medical outcomes (de Jonge et al., 2006; de Jonge & Ormel, 2008) and they frequently conclude that the somatic/affective symptom cluster of depression seems to be more associated with CHD recurrence and mortality than does the cognitive/affective symptom cluster (de Jonge, & Denollet, 2010; De Jonge et al., 2006; Martens, Hoen, Mittelhaeuser, Watkins et al., 2003). These depression symptom groupings however have no theoretical basis, nor are they grounded in any etiological model of depression.

However, when this literature was reviewed recently, there still remains a number of controversies, and the data are not as clear as what seemed to have emerged from the first few publications in this area (Carney & Freedland, 2012). Specifically, Carney and Freedland note that there are a number of methodological challenges remaining in this area, including that somatic and cognitive depression symptoms are classified differently in different publications, that somatic symptoms are far more common than cognitive ones, and are also associated with more severe depression. Finally, they note that many have failed to find that somatic symptoms predict CHD recurrence and that cognitive symptoms do not. All of these issues require a more thorough investigation of this area. Specifically, the use of confirmatory factor analytic methods, rather than exploratory factor analysis (for each data set) would move the field forward, as would allowing items to rest only on one factor (which does not occur currently). The confounding effects of severity of symptoms, and their relative frequency, should also be controlled.

One recent study examined the cardinal symptoms of depression (depressed mood and anhedonia) and their ability to predict CHD recurrence and mortality independent of each other (Davidson et al., 2010). Although depressed mood is classified by most as a cognitive/affective symptom, there is some disagreement about whether anhedonia is a cognitive/affective, or somatic symptom. Interestingly, anhedonia, but not depressed mood, was predictive of increased CHD recurrence and mortality, and this finding has now been replicated in two other studies (Leroy, Loas, & Perez-Diaz, 2010; Pelle, Pedersen, Szabo, & Denollet, 2009). As anhedonia has differing neurobiological mechanisms (Gorwood, 2008), possible causes, including

cytokine-induced ones (Eisenberger, et al., 2010) and intervention directions (Juckel, Sass, & Heinz, 2003), the further investigation of anhedonia in the onset and course of CHD may prove helpful.

Should We Screen for and Treat for Depression in All CHD Patients?

The least evidence-based and most controversial issue in the area of depression and cardiac disease concerns screening. This controversy started in 2008 when the American Heart Association recommended (and the American Psychiatric Association endorsed) (Lichtman et al., 2008) that "screening tests for depressive symptoms should be applied to identify patients who may require further assessment and treatment," if appropriate referral for further depression assessment and treatment is available. Partly in response to this advisory, Thombs et al. (2008) conducted a systematic review of the evidence that screening or treatment improves outcomes of depression or CHD in patients with CHD. They found no trial that tested if depression screening was beneficial in patients with CHD, and the randomized controlled trials of depression treatment provided evidence of only mild improvement of depression symptoms and no improvement in CHD outcome. Therefore, they questioned whether routine depression screening was appropriate.

The proponents for depression screening stated that depression is highly prevalent in CHD patient populations and is clearly a risk marker for increased adverse events as well as decreased quality of life and adherence to treatment (Pozuelo et al., 2009). As there are plausible biological and behavioral mechanisms for this association, and SSRI use improves depression symptoms in other patient populations and is safe in CHD patient populations (see earlier), health-care providers should not hesitate to screen and refer patients for appropriate depression treatment. Pozuelo et al. (2009) cautioned that SSRIs interact with anticoagulants, and bleeding should be monitored closely in patients with CHD who are taking SSRIs. Whooley (2009) argued that, although there are controversial findings in this area, depression screening provided in conjunction with collaborative-care depression management (Unutzer et al., 2002; Rollman et al., 2009) is cost-effective and has a documented positive impact on depression, if not on CHD outcomes. Whooley (2009) noted that there are some costs to screening (e.g., false-positive findings, resulting in stigma for patients incorrectly diagnosed; diversion of health-care resources from other health care needs). However, Whooley suggested that primary-care providers, rather than cardiologists, should conduct depression screening, and patients should undergo screening only when an established collaborative-care-treatment protocol exists. Carney, Freedland, and Jaffe (2009) argued that depression, like age, clearly marks CHD risk, and health-care providers should treat aggressively the readily modifiable CHD risk factors. In addition, because of the strong association between depression and medication nonadherence (Rieckmann et al., 2006), health-care providers should carefully monitor patient adherence to life-saving therapies.

Taking another tack, Shemesh et al. (2009) thought it would be important to document the prevalence of suicidal ideation and intent if the recommendation to screen depression in CHD patient populations was implemented. In a sample of over 1,000 patients with CHD, they determined the prevalence of suicidal ideation (12.0%) and the number of patients who required hospitalization for risk of suicide (0.5%) when routine depression screening occurred in a large cardiology clinic. They concluded that discovery and stabilization of imminently suicidal patients would be a benefit of universal screening, and that there is a high societal cost to neglecting suicidal ideation, intent, and risk in patients with CHD. However, more patients would need immediate thorough psychiatric evaluations for safety, which would affect resource allocation and cost in cardiology clinics.

The main arguments against screening for and treating depression in patients with CHD were the following: (a) there are neither randomized controlled trials nor systematic evidence-based reviews showing that screening for depression or screening for depression and referring for additional treatment sufficiently improves outcomes for depression or CHD, and (b) the existing evidence does not support the recommendation to screen all patients with CHD (Thombs et al., 2008; Thombs, Jewett, Knafo, Coyne, & Ziegelstein, 2009). Furthermore, antidepressant use is associated with only mild improvement in depression symptoms, even in other patient populations (Kirsch et al., 2008) and there has been publication bias (also known as the file-drawer problem) preventing the publication of antidepressant trials with null results (Turner, Matthews, Linardatos, Tell, & Rosenthal, 2008). In addition, considerable health-care resources would be required to mount such a large screening effort, and this resource allocation would be at the expense of other efforts. Finally, the adverse

effects of medications and false-positive results to less-than-perfect screening must be weighed against any benefit that might occur with universal screening (Thombs et al., 2009). In addition to the arguments listed earlier, Ziegelstein,, Thombs, Coyne, and de Jonge (2009), in commenting on the American Heart Association advisory (Lichtman et al., 2008), made the wry observation that there is far greater observational evidence that depressed patients seen in mental-health settings are at risk for CHD incidence and recurrence and that there should be universal screening and referral for CHD in patients with depression. They again contended that the evidence is insufficient to recommend that patients with CHD undergo universal depression screening and referral.

What we require to address this persistent question is a large, definitive depression screening trial, in which patients are randomized to receiving depression screening or not, and then these patients are followed for their depression and CHD outcomes. In doing so, we must also ensure that data are collected on the cost (Frasure-Smith & Lesperance, 2010), the benefit, and even the possible harms associated with recommending depression screening for all patients with CHD.

Will Treating Depression Alter the Course of CHD in Either High-Risk Patients, or Patients with CHD?

This is the most persistent, and perplexing question remaining in the field of depression and heart disease. To some extent, until this question is addressed, the other questions, although scientifically interesting, do not address large public-health concerns. This question cannot be answered through epidemiological studies, animal studies, or any other scientific inquiry; this question can only be answered if we conduct a series of large randomized controlled trials in which patients are randomized to depression treatment, and we determine if this mitigates their CHD recurrence and mortality risk (Whang & Davidson, 2009). A nationwide and/or Centers for Medicare & Medicaid Studies based or randomized controlled trial could be designed and could definitively answer this question. Without these large trials, we are left to wonder: Does depression cause worse prognosis in CHD patients, or is it merely an epiphenomenon?

Conclusion

Although several important conceptual and empirical issues remain to be resolved, the accumulated evidence suggests, at minimum, that depression or depressive symptoms are risk markers for cardiac disease with potentially large implications for public health. In fact, the increasingly refined questions and challenges described herein may be seen as reflections of how much our knowledge about the interconnection between these psychological and medical maladies has advanced in the last three decades. This work also is one more testament to the value of the biopsychosocial approach to health and illness.

Summary and recommendations for treating depression in CVD patients

A variety of depression treatments are effective in depressed CVD patients. Although there is a need to develop more potent depression interventions for CVD patients, the effect size of such treatments with respect to reducing depression is similar in CVD patients as compared to the general population (Thombs et al., 2008). Other than one trial for which the effect of the intervention on prognosis was a secondary outcome (Davidson et al., 2010), depression treatment has not thus far been proven to offset the risk of depression on cardiovascular prognosis. Accordingly, there is a need for additional trials of our most potent depression interventions in CVD patients.

Until these definitive trials have been performed, patients who present with symptoms or signs of depression should be carefully interviewed to assess for the severity of symptoms and the risk of suicide. (See Figure 18.1.) Clinicians can also consider screening all CVD patients for depression; however, current evidence has not verified that this is a cost-effective or beneficial approach (Thombs et al., 2008). Structured depression assessment tools like the Patient Health Questionnaire-9 (Kroenke, Spitzer, & Williams, 2001) comprised of 9 items that ask about the frequency of symptoms used to diagnose depression according to the *Diagnostic and Statistical Manual (DSM-IV)* classification system can be useful supplements to clinical interviews. In addition, serial measurements of depression severity using such tools can be helpful for tracking the effectiveness of depression treatments. Patients with minimal symptoms can be observed with a plan to reassess symptoms at a later date. In contrast, patients with severe symptoms or at risk for suicide should be urgently assessed by a mental-health specialist. Patients with mild to moderate symptoms should be educated about treatment options and should then be asked for their preferred approach. Unless

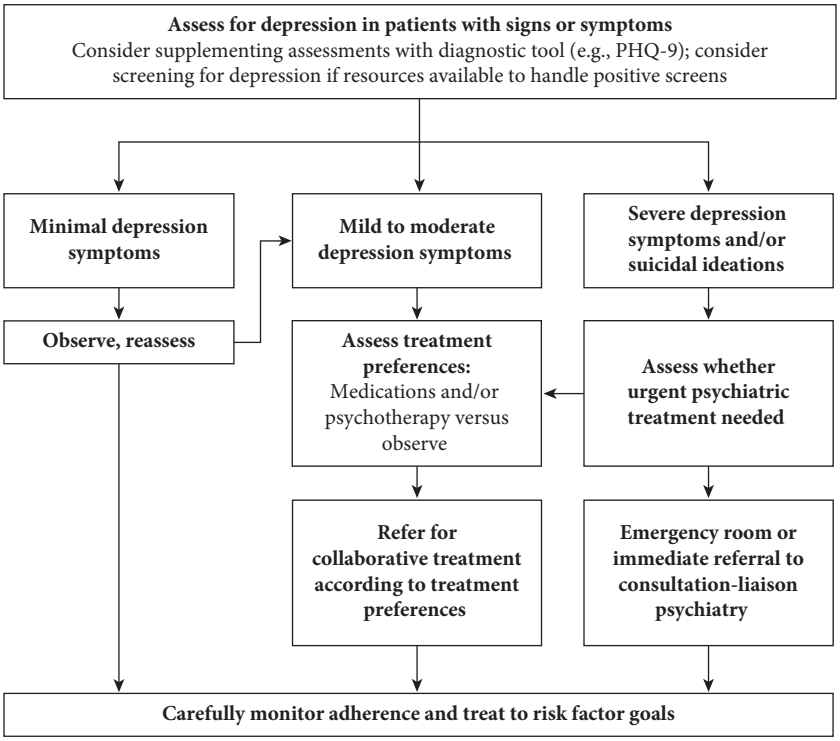

Figure 18.1 Algorithm for managing depression in patients with cardiovascular disease.

patients have severe symptoms or are at risk for suicide, observation with scheduled follow-up remains a reasonable option as depression symptoms may spontaneously remit especially if they developed after acute coronary events. Clinicians will benefit by being informed about the availability and affordability of treatment options in their health-care system, especially nonpharmacologic ones. Ideally, clinicians will have identified mental-health specialists or collaborative care managers with expertise in managing patients with comorbid depression and CVD. With patient preferences in mind, patients can then be referred to appropriate specialists and/or antidepressants can be initiated by the treating provider. Close collaboration with mental-health specialists or other members of the treatment team will be important to ensure that depression treatment is optimized. Clinicians should be cautioned that these recommendations are opinion based, and not evidence based, because neither a depression screening nor CVD outcome randomized trial has been performed yet to directly inform clinical practice.

Other than ensuring that depressed patients are receiving appropriate depression treatment, clinicians should pay special attention to risk factor control and to adherence problems. The use of nonjudgmental language during adherence assessments and possibly, validated adherence assessment tools such as the Morisky Medication Adherence Questionnaire (Morisky, Ang, Krousel-Wood, & Ward, 2008) may facilitate more accurate adherence assessments.

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CHAPTER

19 Cancer and Depression

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Abstract

The authors focus on cancer, a group of medical diseases that have been found to have a robust association with depression. It begins with the etiology of cancers, followed by information about the prevalence of depression among cancer patients and a discussion of shared risk and causal factors of both depression and cancer. The authors then discuss assessment of depression among cancer patients, including diagnostic approaches, methods of detection, and measures of depression. This is followed by a section on psychosocial interventions for depression in cancer patients and clinical practice guidelines.

Key Words: depression, cancer, diagnosis, classification, mental disorder, mood disorders

The importance of focusing on depression and comorbid medical illness is represented by the National Institute of Mental Health's recent commitment to sponsor research that addresses this serious public health problem. For example, between fiscal years 1999 and 2002, funding for depression medical comorbidity research more than doubled, from $8 million to $17 million (Stover, Fenton, Rosenfeld, & Insel, 2003). This is in response to alarming statistics indicating that not only is depression the leading cause of disability among adults in Western countries (Murray & Lopez, 1996) but also comorbid major depression with medical illness increases the odds of dying within a 1-year period by 2.6-fold compared with nondepressed individuals (Kouzis, Eaton, & Leaf, 1995).

The present chapter focuses on cancer, a group of medical diseases that have been found to have a robust association with depression. In terms of the effects of depression on mortality risk for individuals with cancer, in a recent meta-analysis of 76 prospective studies, Pinquart and Duberstein (2010) found that both the diagnosis of depression and higher levels of depressive symptoms predicted elevated levels of mortality. This conclusion was based on investigations that assessed depression before, as well as after, the diagnosis of cancer.

What Is Cancer?

The first description of cancer began with the earliest recordings of history during ancient Egyptian times (American Cancer Society, 2010). The resemblance of finger-like spreading projections of tumors to that of a "crab" likely led Hippocrates, the Greek physician, to describe these tumors using the Greek words *carcinos* and *carcinoma*, which were later translated into the word *cancer*.

Although cancer is often thought of as being a single disease, it is actually a generic term encompassing a group of more than 100 diseases in which the damaged DNA of a cell causes it to grow out of control. The various types of cancer cells can be classified into five broad categories: *carcinoma* (the most common type, a cancerous tumor that begins in the skin or tissue that lines or covers internal organs), *sarcoma* (a cancerous tumor that originates in certain tissues, such as bone or muscle), *leukemia* (cancer in the blood or blood-forming organs),

lymphoma and *myeloma* (cancers that begin in the cells of the immune system, such as white blood cells and plasma cells), and *central nervous system cancers* (those that begin in the tissues of the brain and spinal cord).

The common feature of all types of cancer is the uncontrollable growth and accumulation of abnormal cells. Normal cells behave according to a genetically predetermined set of rules unique to the particular cell type (e.g., skin, blood, brain). These normal cells divide, mature, die, and are replaced systematically. Cancer cell growth differs from normal cell growth. More specifically, due to damaged DNA, instead of dying, cancer cells continue to grow and form abnormal cells that grow more rapidly, in a disorderly fashion, and do not mature correctly. These cells can grow into malignant tumors that replace normal surrounding tissue and spread throughout the body. Whether due to hereditary or environmental causes, cancer involves a malfunction of genes that control cell growth and division. The uncontrolled spread of abnormal cells, or *metastasis*, can affect the functioning of other organs, potentially leading to death.

Cancer Statistics

More than 1.5 million new cases of cancer were expected to be diagnosed in 2010. This estimate excludes basal and squamous cell skin cancers (more than 2 million people were treated for these in 2006) and carcinoma in situ (noninvasive cancer) of any site except urinary bladder. Cancer is the second most common cause of death in the United States, surpassed only by heart disease, but is the leading cause of death worldwide (Farley, Parkin, & Steliarova-Foucher, 2010). In the United States, cancer accounts for nearly one in every four deaths, and in 2010, more than 560,000 Americans were expected to die of cancer; this prediction was confirmed (American Cancer Society, 2010). Slightly less than half of all men and one third of all women in the United States will develop cancer at some point in their lives, with about 78% of all cancers diagnosed in persons 55 years or older.

Prevalence of Depression Among Cancer Patients

Historically, depression has been underdiagnosed and undertreated among cancer patients, possibly due to the belief, among both patients and clinicians alike, that individuals with cancer are "supposed to be depressed" (Massie, 2004). Decades of research refute this belief, suggesting that depression is not an inevitable consequence of cancer. However, it is more prevalent among individuals with cancer than among the general population. In the United States, the estimated lifetime prevalence for major depressive disorder (MDD) is 16.2%, and the point prevalence is 4.5%–9.3% for women and 2.3%–3.2% for men (Kessler et al., 2003; Massie, 2004). However, among individuals with cancer, prevalence rates have been estimated to be to 0%–38% for MDD and 0%–58% for all depression spectrum syndromes.

These estimated prevalence rates demonstrate a robust relationship between cancer and depression but also reflect considerable variation among studies. An important source of this variability is the fact that cancer is not one single disease, as noted earlier. Cancer symptoms, treatments, side effects, and prognosis vary greatly by disease site and therefore can have very different effects on patients' quality of life and experience of depressive symptoms. In addition, some cancers are more common among a particular gender or race, and these cohorts may also have unique genetic, environmental, or behavioral risk factors for both depression and cancer. Finally, differences in study methodology (e.g., how depression is defined, when it is measured), overlap of somatic symptoms, and the inherent difficulty in distinguishing depression from "normal" grief and adjustment to illness further contribute to the variation in depression estimates. The following are depression prevalence rates as a function of differing types of cancer.

Breast Cancer

Breast cancer is the most commonly diagnosed cancer among women and the second most commonly diagnosed cancer overall (Howlader et al., 2011). Although individuals with breast cancer often have a good prognosis, the disease is associated with a particularly high rate of depressive symptoms. For example, in a review of studies published between 1965 and 2002, the rate of depression among women with breast cancer was estimated to be between 1.5% and 46% (Massie, 2004). In part, this variability among studies can be seen as a function of differing methodology. For example, among investigations using depression screening instruments, the rates of depression ranged from 15% to 30%. Among studies that used an actual diagnostic interview, between 5% and 15% of individuals were diagnosed with MDD (Fann et al., 2008).

Prostate Cancer

This form of cancer is the most commonly diagnosed type, occurring at a rate of 156 per 100,000

men (Howlader et al., 2011). Although it is the second-leading cause of cancer death in men, prostate cancer is often slow growing and usually detected at an early stage. As a result, prostate cancer has a very high survival rate (i.e., 5-year survival rate of 99.4%; 10- and 15-year relative survival rates of 98% and 91%, respectively [American Cancer Society, 2012; Howlader et al.]). In comparison to other cancers, relatively little research has focused on the psychosocial aspects of prostate cancer. Although as much as 31% of individuals with prostate cancer report psychological distress, a review of the literature published between 1988 and 2004 found that only 38 studies included a measure of depressive symptomatology, and only 9 of these studies specifically focused on the prevalence of depression as a primary outcome (Bennett & Badger, 2005). Due to methodological flaws and small sample sizes in many of these studies, the authors concluded that there is not enough evidence to draw any definitive conclusions about the prevalence of depression among prostate cancer patients. However, preliminary evidence suggests that the rate of depression among individuals with prostate cancer is likely to be lower than that among individuals with other types of cancer (Salvo et al., 2012).

Lung Cancer

Lung cancer is in the unique position of being very common, having a very poor prognosis, and being very highly associated with depression. Diagnosed at a rate of 62 per 100,000, it is the cancer with the third highest incidence in the United States (Howlader et al., 2011). Lung cancer has a 5-year survival rate of only 15.6%, most likely due to the fact that it is usually not diagnosed until it is at a very advanced stage (Carlsen et al., 2005). Research suggests that lung cancer has the fourth highest estimate of depression among cancer patients, with rates ranging from 11% to 44% (Massie, 2004). In addition, studies consistently indicate that individuals with lung cancer have the highest suicide rate of all cancer patients in both the United States and Europe (Misono, Weiss, Fann, Redman, & Yueh, 2008). It has been suggested that these high rates of depression and suicidality are due to patients' difficulty coping with a particularly poor prognosis. Physical impairment appears to be the greatest risk factor for depression among such individuals (Hopwood & Stephens, 2000).

Cancers of the Oral Cavity and Pharynx

Oropharyngeal cancers, which affect such organs as the tongue, tonsils, and floor of mouth, are among the most common cancers of the head and neck. Collectively, these diseases are the 9th most commonly diagnosed cancer for men and the 14th most commonly diagnosed cancer for women. Due to the location of the cancer, treatments for these types often result in permanent facial disfigurement, as well as problems with eating, drinking, breathing, and speaking (Singer et al., 2012). Research suggests that depression is particularly common among individuals diagnosed with oropharyngeal cancers. A review of studies conducted between 1965 and 2002 found that depressive symptoms were more prevalent among patients with oropharyngeal cancer than among patients with any other type of cancer studied, with rates as high as 57% in some studies (Massie, 2004). Among cancer patients and survivors, those diagnosed with oropharyngeal cancer were found to have the third highest suicide rate (Misono et al., 2008). Although depression rates seem to decrease with the passage of time among long-term survivors of breast cancer, evidence suggests that depression rates among survivors of oropharyngeal cancer remain steady, even years after treatment is completed (Burgess et al., 2005; De Leew et al., 2000). Researchers have proposed that this finding might be related to the high rate of debilitating treatment side effects associated with these cancers.

Pancreatic Cancer

This form of cancer is diagnosed at a rate of 12 individuals per 100,000 per year, making it the 11th most commonly diagnosed cancer in the United States (Howlader et al., 2011). It is also the fourth leading cause of cancer-related death, with a 5-year relative survival rate of 5.5% and a prevalence rate of only 35,000 (Clark, Loscalzo, Trask, Zabora, & Philip, 2010; Howlader et al.). Pancreatic cancer has been found to have one of the highest rates of MDD, estimated to be between 33% and 50% (Massie, 2004). In a large cross-sectional study of patients with 14 common cancers, 28% of individuals with pancreatic cancer reported elevated depressive symptoms on a self-report measure compared with 18.5% of all other patients (Clark et al.). In addition, the suicide rate among patients with pancreatic cancer was found to be 11 times that of the general population (Turaga, Malafa, Jacobsen, Schell, & Sarr, 2011). Despite these alarming statistics, Clark and colleagues (2010) note that in comparison to other cancers, relatively little psychological research has focused on pancreatic cancer, and little is known about the trajectory of depression in this population.

Shared Risk and Causal Factors

Various psychosocial and biological variables have been identified as shared risk and causal factors of both depression and cancer, explaining, in part, the high depression prevalence rate among patients with cancer. Behavioral factors include substance use, sedentary lifestyle, and poor medical adherence, as well as certain demographic and environmental factors, including race and socioeconomic status. Research addressing potential biological mechanisms focus mainly on the role of stress on both the immune and neuroendocrine systems.

Nicotine and Alcohol

Nicotine and alcohol dependence have both been shown to have a very strong association with MDD, although there is not sufficient evidence to determine the direction of causality or whether underlying genetic or environmental factors increase the risk of both substance dependence and MDD (Hasin, Goodwin, Stinson, & Grant, 2005). These substances are also among the most well-known risk factors for the development of cancer. Responsible for at least 30% of all cancer-related deaths, smoking has been linked not only to oropharyngeal and lung cancer but also to cancers of the nasal cavity, pancreas, uterus, ovary, kidney, bladder, stomach, colon, and rectum, as well as acute myeloid leukemia. Alcohol abuse has also been linked to oropharyngeal cancer, liver cancer, and breast cancer, with the risk of cancer increasing significantly with the consumption of more than two drinks per day. In addition, the combination of nicotine and alcohol use increases an individual's risk of oropharyngeal cancers significantly more than does the use of either substance on its own (American Cancer Society, 2011).

Sedentary Lifestyle

There is evidence to suggest that a sedentary lifestyle increases the risk of both depression and cancer. Exercise has long been considered a potential treatment for depression, with some studies demonstrating effect sizes similar to that of evidence-based psychotherapy. Although many early studies suffer from methodological flaws, such as lack of randomization and long-term follow-up, more recent well-controlled trials have demonstrated promising results (Lawlor & Hopker, 2001). In a randomized controlled trial comparing the efficacy of exercise and antidepressants for the treatment of MDD, regular exercise and sertraline produced similar results at a 4-month follow-up (Hoffman et al., 2011). Although neither treatment predicted MDD remission 1 year later, regular exercise during the follow-up did. Exercise has also been used as a treatment for depression specifically among individuals with chronic illness (Herring, Puertz, O'Connor, & Dishman, 2012).

Possible mechanisms of action that might explain the influence of exercise on mood include an increased sense of accomplishment and self-worth, increased social contact and positive feedback from others, and distraction from negative thoughts (Lawlor & Hopker, 2001). Exercise might also increase an individual's resiliency to stress (Salmon, 2001). If regular exercise is an effective treatment for MDD, it stands to reason that it might also serve as a protective factor and that individuals who do not exercise regularly are at an increased risk for depressive symptoms.

Physical activity is associated with a decreased risk of breast cancer, as well as a 20% to 30% decreased risk of colon cancer. Exercise also indirectly decreases the risk of obesity-related cancers, such as myeloma, Hodgkin's lymphoma, aggressive forms of prostate cancer, and cancers of the pancreas, kidney, gallbladder, thyroid, ovary, endometrium, and cervix (American Cancer Society, 2011).

Poor Medical Adherence

Among individuals with chronic illnesses, depressed patients are three times more likely than are nondepressed patients to be nonadherent with treatment recommendations, which can lead to poorer health outcomes (DiMatteo, Lepper, & Croghan, 2000). Mechanisms via which depression might contribute to poor adherence include social isolation, hopelessness, and reduced cognitive functioning, which may make patients less motivated to take care of themselves, less likely to believe that treatment will work, and more likely to forget to take medication (DiMatteo et al.).

Based on current evidence, it is impossible to determine the direction of causality, or if a third variable exists that can lead to both depression and poor adherence. However, it is possible that once a patient develops both a chronic illness and depression, a feedback loop exists in which depression leads to nonadherence and poor adherence leads to a worsening of physical symptoms, which, in turn, leads to a worsening of depression (DiMatteo et al., 2000). To date, no research has specifically examined this potential link between depression and nonadherence in cancer patients. However, it seems likely that poor adherence is one mechanism

by which depression leads to poorer outcomes in this population. In addition, given what is known about health behaviors and cancer risk, it seems possible that noncompliance with recommended diets, exercise, and preventative health care might increase the risk of developing both depression and cancer to begin with, and that it might decrease the likelihood that cancer is diagnosed and treated at an early stage.

Demographic and Socioeconomic Variables

In the United States, the prevalence of depression differs significantly by racial/ethnic group, with research consistently demonstrating that whites have a significantly higher rate of MDD than any other group (Riolo, Nguyen, Greden, & King, 2005). However, the results of the National Health and Nutrition Examination Survey III suggest that this finding is somewhat misleading. This survey of a large (N = 8449) statistically representative U.S. sample found that although MDD is more common among whites, dysthymic disorder is more prevalent among African Americans and Mexican Americans. Given the assumption that chronic depression poses a greater risk of cancer than a single depressive episode (Penninx et al., 1998), the finding that minorities are more likely to experience chronic dysphoria is important.

Results from this survey can also be partially explained by poverty and education. For MDD, poverty was a significant risk factor only for white participants, and lack of education (less than 8 years) was a risk factor only for Mexican American participants (Riolo et al., 2005). However, after controlling for poverty, lack of education was found to be a significant risk factor for dysthymic disorder in all races. An interaction effect was also observed, in which any education above eighth grade was associated with less dysthymia among white participants, but had very little effect for nonwhite participants.

Similar disparities based on race and socioeconomic status (SES) are observed in cancer mortality rates. Although the overall death rate from cancer has been steadily declining over the past two decades, it has decreased much slower in nonwhites than in whites and has not decreased among individuals with low SES (American Cancer Society, 2011). This has resulted in an ever-increasing disparity in cancer mortality.

Cancer mortality is affected by both cancer incidence and cancer survival rates in a given population. The American Cancer Society (2011) notes that individuals with lower SES are at an increased risk of developing cancer because they are more likely to engage in unhealthy behaviors, such as smoking, lack of physical activity, and poor diet, often due to environmental or community barriers that limit opportunities for physical activity and healthy foods. Individuals of lower SES are also likely to experience many barriers to health care, such as lack of health insurance and limited access to preventative care. As a result, they are often diagnosed with cancer at a later stage and are less likely to receive standard treatment. In this manner, many of the same variables that increase the risk of depression (poverty, low education, substance use, sedentary lifestyle) can also increase the risk of cancer. In addition, these variables increase the likelihood that cancer will be diagnosed at a later stage (possibly with more debilitating symptoms and with a worse prognosis) and, subsequently, a greater chance of developing depression in response to cancer.

Although differences in SES can explain many of the mental and physical health disparities among different ethnic groups, discrimination can also play a significant role. Even when insurance status, age, disease, and health status are held constant, nonwhites tend to receive lower-quality health care than whites (American Cancer Society, 2011). This might, in turn, lead to a higher incidence of cancer or a higher incidence in cancer mortality. Perceived discrimination has also been linked to depression, possibly because it is associated with an increased physiological stress response, psychological stress response, and unhealthy behaviors and a decrease in healthy behaviors (Pascoe & Richman, 2009).

Stress, Depression, and Cancer

Biological links between cancer risk and progression have also been identified. Much of this research focuses on the effects of stress on both depression and potential cancer progression, specifically compromised immunological factors.

Cortisol is a glucocorticoid hormone that is produced by the adrenal cortex and regulated by the hypothalamus and pituitary gland. It provides glucose into the blood stream in the face of both physiological and psychological stress in order to supply "fuel" to the individual to engage in the "fight or flight" reaction. However, chronic levels of stress produce elevated levels of cortisol that can lead to depression and immunosuppression. Various types of cancers have been found to have abnormalities in the circadian rhythm of cortisol (Touitou et al., 1995). Such abnormalities are also observed in depressed patients. Moreover, loss of normal

circadian variability in cortisol levels has been found to predict early death among metastatic breast cancer patients (Sephton, Sapolsky, Kraemer, & Spiegel, 2000). On the other hand, psychological treatment aimed at reducing distress has been found to reduce cortisol levels (Cruess et al., 2000). In this light, it is possible that depression-associated abnormalities in cortisol levels may be associated with more rapid cancer progression (Spiegel & Giese-Davis, 2003).

Stress also plays a potential role in cancer growth as a function of its relationship with neuroendocrine correlates. For example, stress hormones may suppress the immune system's ability to resist tumor growth (Callewaert, Moudgil, Radcliff, & Waite, 1991). Rowse, Weinberg, Bellward, and Emerman (1992) found the endocrine system to mediate the effects of psychosocial stressors on mammary tumor growth in mice. Similarly, Sapolsky and Donnelly (1985) found rats to become more vulnerable to stress-induced tumor growth as a function of the effects of glucocorticoids.

In general, data from both animal and human studies suggest that chronic stress and depression can lead to an impairment of the immune response and can promote the initiation and progressions of some types of cancers. These links are potentially mediated by resulting viruses, such as a DNA tumor virus, retrovirus insertion close to a cellular oncogene (i.e., a gene that potentially can cause cancer), and the Epstein-Barr virus (Reiche, Nunes, & Morimoto, 2004). When chronic stress leads to continuous activation of the HPA axis, these mediators can suppress both nonspecific and specific parts of the immune response, such that the system's ability to protect against tumors is compromised.

Depression can also serve as a risk factor for cancer initiation as a function of its relationship with oxidative DNA damage. Oxidative stress occurs when the body is exposed to excessive amounts of electrically charged, aggressive oxygen compounds. These are normally produced during breathing and other metabolic processes, but also in the case of ongoing stress. If the oxidative stress is too high, it overwhelms the body's natural defenses. The aggressive oxygen compounds destroy genetic material, resulting in what are referred to as harmful 8-oxo-guanine base mutations in the DNA. This, in turn, is related to 8-OH-dG levels. In an attempt to better understand the role of depression on cancer progression, Irie, Miyata, and Kasai (2005) found a significant relationship between depression scores and the 8-OH-dG levels in clinically depressed individuals, particularly women. Moreover, both 8-OH-dG levels and depression scores were significant predictors in discriminating between clinically depressed subjects and their gender-matched healthy controls.

Whereas increased attention is being paid to better understand the interrelationships among stress, depression, and cancer risk/progression, variability in types of cancers and various methodological limitations currently renders conclusions tentative. Of particular concern methodologically is the difficulty in determining whether stress or depression "causes" cancer because the transformation of normal cells into clinically malignant ones can involve years after a stressful event or depressive episode occurs.

Assessment of Depression Among Cancer Patients

Much of the challenge in accurately detecting depression among cancer patients lies in the diagnostic criteria itself. For example, depression symptoms are sometimes similar to those of cancer itself, as well as its treatment. These include fatigue, appetite and weight loss, insomnia, loss of energy, and diminished ability to concentrate (Trask, 2004). Although criteria noted in the *Diagnostic and Statistical Manual, Fourth Edition, Text Revision* (*DSM-IV-TR;* American Psychiatric Association, 2000) exclude symptoms clearly and fully accounted for by a general medical condition, such as cancer, a differential diagnosis can be difficult to achieve (Uchitomi, Akechi, Fujimori et al., 2003; Newport & Nemeroff, 1998). The co-occurrence of somatic symptoms in both depression and cancer makes it difficult to distinguish the source, which may lead to misdiagnosis (i.e., false-positives) of depression and inaccurate determination of symptom severity (Akechi et al., 2009; Passik & Lowery, 2011). In recognizing this issue, several researchers have argued that the psychological-cognitive features of depression, such as guilt, hopelessness, and worthlessness, may be more valuable in identifying depressed individuals in a cancer population (Kathol, Mutgi, Williams, Clamon, & Noyes, 1990; Massie, 1989; Reich, 2008).

Diagnostic Approaches

Various diagnostic approaches have been proposed in an attempt to accurately assess depression among patients with cancer, though none are universally accepted (Massie et al., 2011). The etiological approach excludes symptoms attributable to a medical condition; this approach is used in the gold standard assessment tool for depression,

the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I; First, Spitzer, Gibbon, & Williams, 2002; Trask, 2004). No definitive biological markers of depression have been identified in the cancer population and, therefore, the aforementioned issue of differentiation remains problematic (Akechi et al., 2009). It has been argued that the etiological approach may be preferable because it provides a more accurate view of the presence of depression (Rodin, Craven, & Littlefield, 1991). Others contend that the acknowledged problem of distinction may result in underdiagnosis, as well as unnecessary and ineffective interventions. In addition, this approach can be time consuming and, as such, is inefficient in routine clinic utilization (e.g., Akechi et al., 2009; Cavanaugh, 1995; Passik & Lowery, 2011).

Major alternatives to the etiological approach include the inclusive, exclusive, and substitutive approaches. The *inclusive approach* accepts all symptoms of major depression, even if they may be secondary to cancer (Passik & Lowery, 2011; Trask, 2004). This approach uses modified *DSM-IV-TR* criteria and has been described as straightforward, easily implemented, and highly sensitive (Akechi et al., 2009; Newport & Nemeroff, 1998). Although this approach is less likely to result in underdiagnoses due to its high sensitivity, it suffers from low specificity (Kathol et al., 1990). The Research Diagnostic Criteria (RDC; Spitzer, Endicott, & Robins, 1978) and Schedule for Affective Disorders and Schizophrenia (SADS; Endicott & Spitzer, 1978) are two examples of diagnostic interviews that use this approach (Trask, 2004).

In the *exclusive approach*, somatic symptoms of depression that are frequently associated with medical illness, such as fatigue and appetite changes, are eliminated (e.g., Cavanaugh, 1995; Cohen-Cole et al., 1993). The Cavanaugh criteria represent this approach, with the addition of two items: (a) a diminished ability to think or concentrate or indecisiveness and not participating in medical care despite the ability to do so and (b) not progressing despite improving medical condition and/or functioning at a lower level than the medical condition warrants (Akechi et al., 2009; Cavanaugh, 1995). Similar to the inclusive approach, the exclusive approach is considered direct and easily implemented. However, this method is counter to the inclusive approach in that it has increased specificity and lower sensitivity (Trask, 2004).

The *substitutive approach* replaces somatic symptoms with nonsomatic symptoms. For example, cognitive symptoms, such as pessimism, depressed appearance in one's face or body, and social withdrawal, are substituted for symptoms that may be related to physical illness (Akechi et al., 2009; Trask, 2004). Endicott (1984) specified criteria for substitution, though other symptoms may be used (Trask, 2004). When compared with other approaches, the substitutive approach yielded similar prevalence rates to those identified by the inclusive approach and lower rates compared with the etiological approach (Kathol et al., 1990; Trask, 2004).

Researchers have also begun to examine symptom severity as a means of deciphering somatic symptoms among cancer patients. An increased threshold approach applies high symptom-severity thresholds for somatic symptoms of depression (Akechi et al., 2009; Chochinov, Wilson, Enns, & Lander, 1994). While examining cancer-related fatigue and depression, Traeger et al. (2011) concluded that fatigue interference, greater than or equal to fatigue severity, predicted depression among cancer patients. Others have suggested focusing on the severity of cognitive symptoms, such as dysphoric mood, suicidal ideation, and feelings of hopelessness, guilt, and worthlessness, while placing less value on somatic symptoms (Massie, Lloyd-Williams, Irving, & Miller, 2011).

Although no single approach has been established as the most effective in accurately determining which individuals with cancer are actually depressed, the inclusive approach is generally recommended to avoid underdiagnoses and undertreatment (Akechi et al., 2009). Trask (2004) suggested using a comprehensive approach, or combination of approaches, to produce a more accurate estimation but acknowledged that this may be considered overly restrictive for diagnosing depression.

Methods of Detection

Clinical interviews, self-report measures, and brief screening instruments are the chief methods of assessment typically used to identify depression among patients with cancer (Massie, 2004; Trask, 2004). Structured clinical interviews, particularly the SCID-I, are often considered the "gold standard" for assessing depression (Carey, Noble, Sanson-Fisher, & Mackenzie, 2012; Castelli et al., 2011). Clinical interviews are pertinent to ascertaining a diagnosis of depression, but this method is not devoid of conceptual and practical flaws. Clinical interviews are limited by the diagnostic approach on which they are based. For example, criteria comprising the etiological approach, on which the

SCID-I is based, were developed on patients without comorbid physical illness. Interviews can suffer from similar criticisms of the diagnostic approach itself (Trask, 2004). Furthermore, administration of a structured clinical interview requires considerable time and training. Despite these weaknesses, clinical interviews remain the gold standard in the literature against which written self-report measures are compared.

Self-report instruments serve as alternative tools for detecting depressive symptoms in a cancer population. The most popular written self-report measures have demonstrated acceptable reliability, criterion validity, sensitivity, specificity, misclassification rates, and positive predictive value (Trask, 2004). Strengths of this method include quick and easy administration and scoring. Written self-report measures provide gross estimates of the presence and severity of depression but do not warrant diagnosis. Similar to clinical interviews, these measures are subject to the criticisms of the diagnostic approach on which they are based.

With the movement toward the systematic detection of depression has come the utilization of screening tools to quickly and accurately identify patients who may be depressed (National Comprehensive Cancer Network, 2012). As described by Massie and colleagues (2011), screening instruments are not used diagnostically, but rather they serve as an indication of whether patients may suffer from depression. A screening may be followed by a diagnostic assessment before initiating treatment (Akechi et al., 2009; Massie et al.).

Measures of Depression

The following are measures of depression commonly used among various cancer patient populations.

HOSPITAL ANXIETY AND DEPRESSION SCALE

The Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983) is a 14-item, self-report scale containing two subscales, depression and anxiety, each comprised of seven items with scores ranging from 0 to 21. The HADS has been favored among other measures due to its validation in a medically ill population and removal of the somatic features of depression (Carey et al., 2012; Castelli et al., 2011). The developers of the scale suggested interpreting subscale scores of 0 to 7 as normal, 8 to 10 as mild, 11 to 14 as moderate, and 15 to 21 as severe depression (or anxiety) but did not provide evidence for the support of the thresholds (e.g., sensitivity and specificity; Carey et al., 2012). Several studies have examined the use of the HADS as a screening tool for depression, although no definitive optimal cutoff score has been established (Carey, Noble, Sanson-Fisher, & Mackenzie, 2012);Vodermaier, Linden, & Siu, 2009; Walker et al., 2007). As the measure has been frequently evaluated as a means of discriminating "depression caseness," a full review is beyond the scope of this chapter. However, Walker and colleagues (2007) published a summary of studies evaluating the effectiveness of the HADS in doing so. Using receiver operating characteristic (ROC) curves, these researchers determined a cutoff of 14/15 to be optimal in a sample of outpatients diagnosed with varying types of cancers. Although further research is necessary to define the optimal threshold determining caseness, current reviews of the literature suggest 8 to be the most common cutoff score and lowest threshold for identifying a probable case of major depression (Carey et al., 2012; Pirl, 2010).

THE CENTER FOR EPIDEMIOLOGICAL STUDIES–DEPRESSION SCALE

The Center for Epidemiological Studies–Depression Scale (CES-D; Radloff, 1977) includes 20 items with scores ranging from 0 to 60. This self-report measure generally takes less than 5 minutes to complete. It is recognized for the minimal emphasis it places on somatic symptoms, though some physical symptoms are included. This measure has been validated in mixed samples of cancer patients with sound sensitivity and specificity (Vodermaier et al., 2009). According to Pirl (2010), scores of 16 or greater suggest a probable case of major depression.

BECK DEPRESSION INVENTORY

The Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) is a 21-item self-report scale frequently used in the general population to evaluate the severity of depression. Scores range from 0 to 63, with 10 or greater suggestive of at least mild major depression (Pirl, 2010). The BDI-II (Beck, Steer, & Brown, 1996) was developed to replace earlier versions and mimics changes in criteria for major depression from the *DSM-III* (American Psychiatric Association, 1980) to the *DSM-IV* (American Psychiatric Association, 2000;. The BDI-II places less emphasis on somatic symptoms than the BDI, which may reduce the number of false-positives.

Patient Health Questionnaire-9

This Patient Health Questionnaire-9 (PHQ-9; Kroenke, Spitzer, & Williams, 2001) self-report measure consists of those nine items from the Patient Health Questionnaire (PHQ; Spitzer, Kroenke, & Williams, 1999) that address depression and is based on the diagnostic criteria for MDD contained in *DSM-IV-TR*. The PHQ-9 is a brief, self-report diagnostic screening tool developed for use in primary care settings and medical specialty populations, including cancer (Kroenke et al.). It assesses depressive symptoms, functional impairment, and depressive severity; a diagnostic algorithm can be applied or the measure can be used as a continuous scale. An individual is considered likely to meet criteria for MDD if one or both items pertaining to low mood and anhedonia are endorsed along with at least five other symptoms for "more than half of the days" (for the item related to suicide, "several days") and a functional impairment that is at least "somewhat difficult." Scores greater than 15 indicate possible depressive disorder. Unfortunately, evaluations of the diagnostic accuracy of the PHQ-9 in a cancer population are sparse (Vodermaier et al., 2009). In one study conducted by Thekkumpurath and colleagues (2011), the PHQ-9 accurately detected MDD in cancer patients when used as a continuous measure with a cutoff of 8 or greater.

Psychosocial Interventions for Depression in Cancer Patients

A plethora of studies have been conducted over the past several decades that have evaluated the efficacy of various psychosocial interventions for cancer patients. Many of these have targeted psychological distress in general, as well as depression in particular (Nezu & Nezu, 2007). Interventions have included various types of strategies usually included under the large umbrella of cognitive and behavioral therapies (e.g., cognitive therapy, behavioral activation, problem-solving therapy (PST), behavioral stress management), as well as psychodynamic psychotherapy, supportive therapy, counseling, and psychoeducation. Because of this large number of investigations, multiple reviews and meta-analyses have also been conducted to assess the overall impact and efficacy of such treatment approaches (e.g., Rodin, Lloyd, Katz, Green, Mackay & Wong, 2007; Williams & Dale, 2006). Unfortunately, due to a number of factors, including the variability of patient-related characteristics (e.g., differing disease types, status, and treatments), as well as the less than stellar quality of the methodological rigor with which many of these studies have been conducted (e.g., low numbers of participants, inadequate control against threats to internal validity), it is difficult to draw any definitive conclusions about this literature (Jacobsen, 2009).

Results From Meta-Analyses and Systematic Reviews

A recent example of the lack of agreement among health care professionals about this issue involves a series of articles published in 2006 in the *Annals of Behavioral Medicine* that represents a debate that occurred the previous year at the Annual Meeting of the Society of Behavioral Medicine in Boston (Stefanek, Jacobsen, & Christensen, 2006). In essence, proponents of one "side" of the argument suggested that psychological interventions for patients with cancer are, in fact, ineffective (Coyne, Lepore, & Palmer, 2006; Lepore & Coyne, 2006), whereas the other side argued that they are efficacious (Andrykowski & Manne, 2006; Manne & Andrykowski, 2006). The debate essentially centered around the scientific quality of the methodology used in scores of published studies, whereby of the entire pool of studies testing the efficacy of psychological interventions to treat distress in cancer patients, Coyne & Lepore (2006) argued that because, in their opinion, only two such investigations that found treatment to be effective were of acceptable high quality (i.e., Greer, Moorey, & Baruch, 1992; Nezu, Nezu, Felgoise, McClure, & Houts, 2003), there was insufficient data to conclude that, *in general*, psychological treatments are effective. With specific regard to depression, Rodin et al. (2007) came to a similar conclusion indicating that their systematic review found limited evidence for the effectiveness of psychosocial interventions for depressed cancer patients.

In addition, after conducting a systematic review of 15 randomized controlled trials (RCTs) judged to be of at least "fair" methodological quality, Newell, Sanson-Fisher, and Savolainen (2002) concluded that none of the 13 approaches studied merited a tentative recommendation, although cognitive-behaviorsl therapy and guided imagery were judged to merit further exploration. Sheard and Maguire (1999) conducted two meta-analyses and found (a) a small effect size ($d = .36$) for psychosocial treatments for depression based on 20 investigations and (b) that the magnitude decreased to .19 when 3 of these studies were eliminated from the second analysis because they were considered to be methodologically weak.

On the other hand, Devine and Westlake (1995), based on their meta-analysis of 98 studies, concluded that psychoeducational interventions are of benefit to adults with cancer and depression. More specifically, they reported a medium effect size across studies of $d = .54$. Similarly, Barsevick et al.'s (2002) systematic review of 36 investigations concluded that psychoeducational interventions reduced depressive symptoms in patients with cancer and that behavior therapy alone or in combination with education is beneficial. Osborn, Demoncada, and Feurerstein (2006) further reported a large effect size ($g = 1.21$) regarding cognitive-behavioral therapy across five studies. Williams and Dale (2006) attempted to differentiate between studies that used depressive symptoms as the outcome variable (a continuous variable) as contrasted to depression as a diagnostic entity (a categorical variable). In doing so, they concluded that 7 of 10 RCTs (using cognitive-behavioral therapy as the treatment approach) provided evidence in support of psychological interventions being beneficial for reducing depressive symptoms, whereas three of four RCTs were supportive when depression was treated as a diagnostic entity.

The collective conclusion from these meta-analyses and reviews suggests that whereas some evidence is supportive of the potential efficacy of psychological interventions for the treatment of depression and depressive symptoms, the question is far from resolved. In part, this state of affairs depends on the criteria one uses to critically assess the findings. As noted above, the two sides of the debate involved in the *Annals of Behavioral Medicine* articles reviewed essentially the same set of studies and came to opposing conclusions. It is no wonder that the majority of the meta-analyses and systematic reviews conclude with a call for additional studies to be conducted that are methodologically sound (e.g., adequate numbers of participants to allow for sufficient statistical power, adequate methodological controls, including comparison conditions). The present authors wholeheartedly agree with this sentiment (see also Moyer, Sohl, Knapp-Oliver, & Schneider, 2009).

Psychological Interventions to Treat Depression and Depression Symptoms

To provide the reader with an illustration of the various types of interventions applied to impact distress and/or depression among adult cancer patients, we provide a brief description of a few such approaches.

COGNITIVE THERAPY

Cognitive therapy is based, in part, on the premise that inaccurate beliefs and maladaptive information processing have a fundamental role in depression and correcting such maladaptive thinking serves to reduce distress (DeRubeis, Siegle, & Hollon, 2008). Savard and colleagues (2006) conducted an RCT examining the effect of cognitive therapy for depression in women with metastatic breast cancer. The women were encouraged to develop an optimistic, but realistic, attitude toward their situation, as opposed to a negative (e.g., only thinking about death) or overly positive attitude (e.g., hoping to be cured). The women in the cognitive therapy condition, which lasted for eight weekly sessions plus three booster sessions, were also trained to identify negative thoughts and use cognitive restructuring to alter dysfunctional cognitions about cancer and other life situations. Compared with a wait-list control (WLC) group, those who received cognitive therapy reported significantly lower depression scores on one measure at posttreatment, and reduced depression scores, though not statistically significant, on two additional measures. Treatment gains were maintained at a follow-up assessment, which may have been attributed to the booster sessions included in the treatment protocol.

COGNITIVE-BEHAVIORAL STRESS MANAGEMENT

Consisting of both didactic and treatment components, cognitive-behavioral stress management (CBSM) is designed to reduce stress and distress using a variety of techniques, including the effective implementation of coping strategies to manage daily cancer-related stressors, relaxation strategies (e.g., progressive muscle relaxation and guided imagery), enhancement of social resources, stress response monitoring, and cognitive restructuring skills for use when thinking negatively. Antoni and colleagues (2001) conducted an RCT to evaluate a 10-week group-based CBSM treatment for women with early-stage breast cancer. Researchers concluded that the CBSM intervention served to reduce the prevalence of moderate depression and to increase optimism and benefit finding (i.e., identifying positive aspects of a traumatic event).

PROBLEM-SOLVING THERAPY

PST promotes the adoption and effective application of adaptive problem-solving attitudes and skills to solve stressful problems in everyday living, particularly those associated with major stressful

events, such as cancer and its treatment (Nezu, Nezu, & D'Zurilla, 2013). Nezu, Nezu, Felgoise, McClure, and Houts (2003) conducted an RCT, entitled Project Genesis, to assess the efficacy of PST in reducing significant distress among adult cancer patients. Participants were randomly assigned to an individual PST condition, a PST condition that included the patient's significant other, or a treatment as usual (TAU) condition. The inclusion of the PST condition that included a significant other served as a means to assess the beneficial effects of a formal social support system, where the role of the significant other was conceptualized as a "problem-solving coach." Across several self-report, clinician ratings, and ratings by significant others, focused heavily on depression, results at posttreatment provided solid evidence for the support of the overall efficacy of PST for decreasing emotional distress and enhancing global quality of life. Patients in both PST conditions were found to show significant improvements in depression and overall distress compared with the control condition, with no differences found between the two PST conditions at posttreatment. However, at the 6-month follow-up, those in the PST condition that included significant others showed statistically and clinically significant improvements beyond those who received PST individually.

BEHAVIORAL ACTIVATION

The goal of behavioral activation is to increase a patient's overt behaviors that are likely to connect him or her with reinforcing environmental contingencies to generate corresponding improvements in thoughts, mood, and overall quality of life (Hopko, Lejuez, Ruggiero, & Eifert, 2003). Behavioral activation treatment for depression (BATD) propagates nondepressed behavior through guided behavioral scheduling and avoidance reduction strategies. Within a population of breast cancer patients diagnosed with MDD, Hopko and colleagues (2011) conducted an RCT comparing behavioral activation for depression (BATD) with PST. Results indicated that both BATD and PST led to significant pre–post improvements across various clinical, functional, and patient satisfaction outcomes. Of specific relevance, large effect sizes were reported on all depression outcome measures across both treatments and treatment gains were maintained at 12-month follow-up. Not only did this study indicate that PST is an effective approach, but that BATD can be a viable alternative to help decrease depression among patients with cancer as well.

MINDFULNESS-BASED STRESS REDUCTION

Mindfulness-based stress reduction (MBSR) teaches individuals to use various meditation strategies, such as being mindful (i.e., purposefully attending in a nonjudgmental manner to the experience of a present moment) of one's breathing and other sensations while sitting and walking, mindful movement through certain yoga postures, and body scan during which attention is sequentially directed throughout the body (Hofmann et al., 2010; Kabat-Zinn, 2003). MBR is a group-based program typically consisting of eight weekly sessions, each lasting 2.5 hours, in addition to one full-day retreat and daily at-home practice. Based on a small number of RCTs, MBSR appears to be an efficacious intervention for reducing depressive symptomatology among patients with cancer (e.g., Hoffman et al.).

MINDFULNESS-BASED COGNITIVE THERAPY

Mindfulness-based cognitive therapy (Segal, Williams, & Teasdale, 2002) represents a combination of MBSR and aspects of cognitive therapy (e.g., a focus on the impact of cognitive patterns on current functioning) and has been modified for a cancer population and evaluated via an RCT (Foley, Baillie, Huxter, Price, & Sinclair, 2010). Adaptations included the addition of didactic information about common challenges associated with cancer and additional options for the practice of meditation (e.g., graded practice to accommodate psychological avoidance of the cancer site during the body scan meditation and variant postures, length and form of home practice). Compared with a WLC, the MBCT intervention yielded large and significant improvements in depression in a mixed sample of cancer patients.

COLLABORATIVE CARE

Generally, collaborative care involves the employment of care managers to aid in the management of patients through a structured and systematic delivery of multifaceted organizational interventions (Bower, Gilbody, Richards, Fletcher, & Sutton, 2006). Such interventions for depressed cancer patients include a depression screening to identify cases, treatment using an evidence-based protocol, structured collaborations between oncologists, primary care providers, and mental health specialists, and active monitoring of outcomes and adherence to treatment (Jacobsen, 2009). One such approach, Alleviating Depression Among Patients With Cancer (ADAPt-C), conducted by Ell and

colleagues (2008), included 472 low-income, depressed, predominantly Latina patients randomly assigned to either a collaborative care intervention or an enhanced TAU. In this approach, PST was included as the main psychosocial treatment due to its established efficacy among depressed cancer patients, its feasibility, acceptability, and adaptability to cancer-specific, educational, and sociocultural factors (Dwight-Johnson, Ell, & Lee, 2005). Compared with baseline assessments, more than half of the patients receiving the ADAPT-C intervention reported a 50% or greater reduction in depressive symptoms 1 year later; improvements were also significant regarding quality-of-life outcomes, as well as emotional, functional, and physical well-being.

A second large collaborative care intervention (Depression Care for People with Cancer [DCPC]; Walker & Sharpe, 2009) has been implemented in a population of cancer patients with MDD in the Symptom Management Research Trials (SMaRT) oncology series of RCTs (Strong et al., 2008). Two hundred participants were randomly assigned to usual care or usual care plus intervention in which a cancer nurse provided psychoeducation and PST and communicated with oncologists and primary care physicians about the management of MDD. Results indicated that those who received the collaborative care intervention reported significantly lower scores on a measure of depression at 3-month posttreatment, with 68% compared with 45% remitted in the usual care condition; benefits were maintained at 6-month and 1-year posttreatment.

Clinical Practice Guidelines

Unfortunately, despite the high levels of emotional distress, including depression, that is experienced by cancer patients, psychosocial care within the greater medical profession was not considered systematically to be a crucial aspect of quality cancer care until a report by the Institute of Medicine (IOM) was published titled "Cancer Care for the Whole Patient" (Adler & Page, 2008). In part, this report was based on the pioneering efforts of a panel and set of guidelines set forth by the National Comprehensive Cancer Network (NCCN). The NCCN is a not-for-profit alliance of 21 of the world's leading cancer centers that is dedicated to improving the quality and effectiveness of care provided to patients with cancer. The NCCN panel focusing on distress management began in 1997 and was interdisciplinary in nature. The most recent NCCN guidelines for distress management is Version 3.2012 (National Comprehensive Cancer Network, 2012).

In general, the following components are suggested by NCCN as a model of the effective delivery of psychosocial health services that could be implemented in any community oncology practice (2012):

1. Screening for distress and psychosocial needs
2. Developing and implementing a treatment plan to address such needs
3. Referring to psychosocial care services as needed
4. Reevaluating outcome and readjusting plan if appropriate.

The NCNN defines "distress" as "a multifactorial unpleasant emotional experience of a psychological (cognitive, behavioral, emotional), social, and/or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms and its treatment. Distress extends along a continuum, ranging from common normal feelings of vulnerability, sadness, and fears to problems that can become disabling, such as depression, anxiety, panic, social isolation, and existential and spiritual crisis" (p. DIS-2).

Clinical Guidelines: Screening for Depression

As a general recommendation, the NCCN suggests that all patients should be screened for distress at an initial visit, as well as at appropriate and clinically relevant intervals. To this end, they developed a simple "distress thermometer" that requests individuals to circle a number (from 0, indicating *no* distress, to 10, representing *extreme* distress) in order to describe how much distress they have been experiencing during the past week. This measure has been validated with various cancer patient populations and found to be concordant with the HADS (Mitchell, 2007), as well as displaying acceptable accuracy, sensitivity, and specificity in comparison to the CES-D (Ransom, Jacobsen, & Booth-Jones, 2006). As such, this distress thermometer can serve as an accurate and user-friendly screening for emotional distress as a precursor to additional evaluation for depression (e.g., if distress levels are high).

In addition, the NCCN developed a problem list that goes hand-in-hand with the distress thermometer that contains 38 items representing common problems experienced by patients with cancer. Within a subsection of "emotional problems," depression is listed. Using both tools can provide for

an important initial approach to screen for depression. Along these lines, given if a cancer patient provides responses consistent with possible clinically significant symptoms of depression, the clinician can follow up with additional self-report measures, such as those described earlier in this chapter (e.g., HADS, BDI-II, PHQ-9).

Clinical Guidelines: Treating Depression

As noted earlier, due to the variability in the quality of published studies that evaluated one or more psychosocial approaches to treating depression, there are no strong consensus guidelines to help direct the average clinician regarding choice of an intervention. However, based on the overall literature base, the IOM report identified several types of psychotherapies that have significant potential. These include cognitive-behavioral therapy, supportive psychotherapy, and family/couples therapy.

Of greater aid is the evidence-based approach that Jacobsen, Donovan, Swaine, and Watson (2006) used in an attempt to develop a set of treatment recommendations. Of particular importance is the identification of more recent studies, many of which tend to be of higher methodological quality than their antecedents of several decades earlier, as well as the classification of recommendations by disease status (e.g., newly diagnosed, terminal phase), treatment status (e.g., patients undergoing chemotherapy, surgery, or radiotherapy), type of intervention (e.g., relaxation techniques, PST, supportive-expressive therapy), and intervention type by disease or treatment status. These efforts go a long way to summarizing the extant empirical literature for mental health professionals working with adult cancer patients. With regard to type of treatment approaches to choose among, these authors identified the following as being backed by empirical support: relaxation techniques, psychoeducation, supportive and supportive-expressive therapies, PST, counseling, and cognitive therapy. It should be noted that these authors appropriately acknowledge the existence of significant limitations regarding such guidelines and caution the reader along these lines (e.g., some recommendations are based on a very small number of studies).

Summary and Future Research

The relationship between cancer and depression is robust. Although rates of depression vary as a function of certain patient and disease factors (e.g., ethnicity, type of cancer, stage of cancer), the prevalence of clinical depression and high levels of depressive symptoms among individuals with cancer remain high. As with most medical diseases that are associated with high levels of depression, it is underdetected, underdiagnosed, and undertreated among cancer patients. Another factor that influences the variability in identified prevalence rates involves the differences in how depression is defined (symptoms versus diagnosis), which assessment methods are used (clinical interviews versus self-report measures), and at what point in time it is assessed (differing cancer stages).

Various psychological and biological factors have been the focus of empirical study in terms of possible shared risk and causal factors. These include substance abuse, sedentary lifestyle, poor medical adherence, ethnicity, SES, discrimination, the effects of stress on the immune and neuroendocrine systems, and oxidative DNA damage.

Although scores of studies have been conducted that have evaluated a wide range of differing types of psychological and psychosocial interventions, little consensus exists in the field regarding the overall efficacy of these approaches. Whereas a group of meta-analyses and/or systematic reviews conclude that psychological treatments are effective for reducing depression, others conclude the opposite. Of particular concern involves the effects of such interventions on improving survival rates. The field is also equivocal on this specific issue as well, with some researchers pointing to data indicative of reduced mortality resulting from participating in a psychological treatment (e.g., Andersen et al., 2008). On the other hand, Stefanek, Palmer, Thombs, and Coyne (2009) point to significant methodological flaws in this study, asserting that, as such, no support thus far exists for the survival benefits attributable to psychosocial interventions. As such, it would appear that the debate continues (Nezu, Nezu, Felgoise, & Greenberg, in press).

Given the lack of consensus in the field regarding these issues, we offer the following recommendations regarding future research:

1. More research should be conducted regarding efficacious interventions to improve the quality of life and reduce depression among cancer patients and their families.
2. More research should be conducted regarding the effects of psychosocial interventions on health outcome (i.e., does reducing depression also prolong survival?).
3. Such research needs to be more methodologically rigorous (e.g., include adequate

control groups, use manualized protocols, assess for treatment integrity, use more multimodal assessment procedures).

4. Conduct component analyses of the intervention studies to help answer such questions as, "Which treatment components are responsible for the actual improvement in symptoms?"

5. Identify important moderators of treatment efficacy (e.g., race, age, gender, cultural background, severity of symptoms, number of symptoms).

6. Identify important mechanisms of action (e.g., cognitive, emotional, behavioral, neuroendocrine, immune system).

7. Improve treatment implementation and access to such treatment.

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CHAPTER

20 Pain

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Abstract

Depression and pain are commonly comorbid and often disabling conditions. This chapter reviews current evidence regarding the extent of comorbidity of these two conditions across different settings. The authors briefly summarize popular theories regarding the frequently disputed causal nature of the pain-depression relationship and address the implications of comorbid pain and depression with regard to treatment outcomes and symptom presentation. Additionally, key shared neurobiological substrates consistent with the symptom presentation and the covariation of pain and depression are discussed. The chapter concludes with a summary of a variety of treatment approaches currently employed in the treatment of pain and depression as well as empirical evidence concerning the efficacy of these various approaches.

Key Words: chronic pain, depression, comorbid pain, comorbid depression, neurobiological substrates of pain and depression, treatment

Introduction

Pain is a universal experience affecting men and women of diverse age groups, races, cultural backgrounds, sexual orientations, socioeconomic status, and various other characteristics. The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Merskey, 1986, p. 51). Given its multidimensional and subjective nature, pain represents a ubiquitous yet often perplexing experience. Although pain is experienced universally, it is experienced in a very unique manner by each individual. Frequently health care providers are unable to administer objective measures to assess pain; they may find that the severity of an individual's pain report is disproportionate to the extent of tissue damage or physical injury, or they may find that treatment responses are variable between patients and even within a single patient (IOM, 2011). These idiosyncrasies underscore the importance of understanding pain from a holistic and multidimensional perspective, beyond the mere physical attributes of tissue damage or injury. Moreover, several variables may serve to amplify or temper the intensity and unpleasantness of pain sensation. These may include biological, psychological, and social factors (IOM, 2011). Accordingly, chronic pain can be best understood from a biopsychosocial perspective through which pain is viewed as a complex, multifaceted experience emerging from the dynamic interplay of a patient's physiologic state, thoughts, emotions, behaviors, and sociocultural influences. In the last several decades, advancements in pain research have drastically improved our understanding of pain processing, factors that maintain pain, mediators of pain perception, and reciprocal effects of comorbid conditions.

It is a well-established fact that pain primarily serves an adaptive, protective function; the

unpleasant nature of pain alerts and motivates us to react in response to a harmful or noxious stimulus, such that it may prompt withdrawal, seeking protection of damaged tissue, seeking medical attention and care, and/or engaging in avoidance behaviors. Nevertheless, uncontrolled and prolonged pain may alter an individual's physiology and manifest as chronic pain. Chronic pain is typically differentiated from acute pain based on its persistence—that is, via temporal classification. Pain may be further distinguished based on etiology (e.g., malignant versus nonmalignant pain), physiologically (e.g., nociceptive pain versus neuropathic pain), or based on physiologic maintenance mechanisms (e.g., pain that is thought to emerge as a result of peripheral and central reorganization). Generally, it is accepted that pain that persists beyond the expected period of time for tissue healing following an injury or surgery represents chronic pain. The specific time frame constituting an expected healing period is variable and often difficult to ascertain. For ease of classification, certain guidelines suggest that pain persisting beyond a three-month time window is considered chronic pain (Merskey & Bogduk, 1994). Nevertheless, classification of pain based solely on duration is a strictly practical and, in some instances, arbitrary criterion.

In 2011, the Institute of Medicine reported that, in the United States alone, approximately 116 million adults are affected by chronic pain conditions (IOM, 2011). The combined direct and indirect estimated cost of chronic adult pain alone amounts to $560 to $630 billion annually (IOM, 2011). Pain remains one of the most common concerns brought to the attention of health care professionals (Abbot & Fraser, 1998; Crook, Rideout, & Browne, 1984). Increased reports of emotional distress (e.g., depression, anxiety, and frustration), increased rates of pain-related disability, pain-related alterations in cognition, and reduced quality of life exemplify the widespread implications of chronic pain. Pain can be disabling in various respects, including emotionally, physically, functionally, and occupationally. Pain-related disability has been found to have a strong association with poor health, greater medication and health care utilization, depression, and more widespread pain, especially in individuals who report high levels of pain intensity (Tripp, VanDenKerkhof, & McAlister, 2006). A study conducted by Stewart and colleagues found that during a two-week period, 13% of the U.S. workforce reported a loss of productivity due to a common pain condition (Stewart, Ricci, Chee, Morganstein, & Lipton, 2003). Another study reported that, in its sample, 26% of chronic pain patients endorsed an adverse impact on their employment and 19% reported having lost their jobs as a result of the negative impact of pain on their occupational functioning (Breivik, Collett, Ventafridda, Cohen, & Gallacher, 2006). Emotional distress frequently intensifies as pain becomes more intractable or as it progressively interferes with various domains of life, including social, recreational, and occupational domains. Thus, it is not surprising that an increased prevalence of psychiatric disorders (e.g., depression, anxiety) exists among individuals with chronic pain.

Comorbid Pain and Depression

Chronic pain and depression are highly comorbid conditions; comorbidity rates have been estimated to range from 30% to 50%, varying according to the population under study, the setting of assessment, and the assessment methods employed (Bair, Robinson, Katon, & Kroenke, 2003; Kroenke, 2005; Miller & Cano, 2009). For instance, one review study of chronic pain patients reported an increased prevalence of depression that varied substantially according to setting, such that prevalence estimates ranged from 18% in population-based settings, to 27% in primary care settings, to 38% in psychiatric clinics, to 52% in pain clinics, and to 56% in orthopedic or rheumatology clinics (Gambassi, 2009). Furthermore, the lifetime prevalence of major depression doubles or triples in individuals suffering from pain as compared with pain-fee individuals, characterized by a stronger association as the severity of pain increases (Gambassi, 2009; Patten, 2001). Conversely, studies have reported that, in patients with depression, the prevalence of pain ranges from 15% to 100%, with an estimated mean prevalence of 65% (Gambassi, 2009). A cross-national study including 15 countries revealed that, in primary care patients, a bidirectional relationship between persistent pain and psychological disorder (anxiety and/or depressive disorder) exists (Gureje, Simon, & Von Korff, 2001). That study found that this relationship appears to be symmetrical, such that there is a comparable likelihood of persistent pain or psychological disorder being the antecedent to the other (Gureje et al., 2001). Notably, impairment of daily activities emerged as the strongest predictor of onset for either condition (Gureje et al., 2001). In a longitudinal study of aging among 3,654 older adults, pain at baseline was an independent predictor of depression two years later, OR = 1.54; similarly,

depression at baseline represented an independent predictor of onset of pain two years later, OR = 1.45 (Torta & Munari, 2010).

Previously depressed patients have been found to have an increased risk of developing various pain conditions (e.g., musculoskeletal pain, headache, chest pain, abdominal pain) later in life, with the twofold risk association remaining significant up to eight years later (Forseth, Husby, Gran, & Forre, 1999; Hotopf, Mayou, Wadsworth, & Wessely, 1998; Leino & Magni, 1993; Magni, Moreschi, Rigatti-Luchini, & Merskey, 1994; Von Korff, Le Resche, & Dworkin, 1993). Low back pain reports are twice as frequent in depressed individuals as in nondepressed individuals, and depressive symptoms have been found to predict onset of future musculoskeletal pain (Gambassi, 2009). Research has demonstrated that depressed mood reduces pain threshold and increases multiple components of pain perception. Consequently depression in chronic pain patients is associated with greater pain intensity, increased pain persistence, pain-related disability, and increased use of maladaptive coping strategies, such as passive and avoidance strategies and lower perceptions of control (Fisher, Haythornthwaite, Heinberg, Clark, & Reed, 2001).

Frequently, depressive symptoms include somatic complaints (e.g., sleep disturbance, motor retardation or agitation, loss of energy, changes in appetite and weight); however, somatic complaints endorsed by individuals may or may not be related to cognitive and affective complaints, which can complicate the disentanglement of comorbid pain and depression. Notably, it appears that pain may account for more than half of all somatic complaints in primary care patients with depression (Kroenke, 2003). These statistics substantiate the importance of consideration and thorough assessment of depression symptoms *and* pain complaints when the presence of either is suspected. According to data collected by the World Health Organization (WHO) from 14 countries, 69% (range 45% to 95%) of patients with depression presented with somatic complaints solely, with pain representing the most common somatic symptom reported (Simon, VonKorff, Piccinelli, Fullerton, & Ormel, 1999). Interestingly, a factor analytic study of the Beck Depression Inventory II (BDI-II) conducted by Morley and colleagues revealed that, in a large sample of chronic pain patients, two factors emerged: one reflecting items relating to somatic and physical function and a second factor composed of items relating to a negative view of the self, with moderate and low scores on these two factors, respectively (Morley, Williams, & Black, 2002). These research findings demonstrate the intricacy encountered in distinguishing somatic depression and chronic pain complaints without further assessment. Based on a study of 132 chronic pain patients (44 with comorbid major depression), Geisser and colleagues concluded that both the BDI and the Center for Epidemiological Studies-Depression Scale (CES-D) significantly discriminated between chronic pain patients with and without major depression and optimal cutoff scores for each measure were statistically determined (BDI $\geq$ 21, CED-D $\geq$ 27) (Geisser, Roth, & Robinson, 1997). Importantly, their results indicated that removal of the somatic items on each scale did not improve discriminative ability (accuracy of classification) of either instrument (Geisser et al., 1997). Such findings highlight the fact that depression and pain significantly and uniquely contribute to variance in the scores of each measure; these conclusions further reinforce the notion that, in medical populations, higher cutoff scores are necessary to better ensure higher diagnostic accuracy.

Functional somatic syndromes exemplify how comorbid depression and pain may manifest and interact. Examples of functional somatic syndromes include chronic fatigue syndrome, fibromyalgia, and irritable bowel syndrome (IBS). These conditions are characterized by a collection of somatic complaints that cannot clearly be attributed to organ pathology, yet the symptoms are highly disruptive to the lives of afflicted individuals. Pain represents the chief somatic complaint, whereas the primary emotional symptom experienced in functional somatic syndromes is depression (Goldenberg, 2010). The incidence of depression is approximately 30% in fibromyalgia populations and of similar magnitude in IBS populations (Arnold et al., 2006; Cole, Rothman, Cabral, Zhang, & Farraye, 2006; Kato, Sullivan, Evengard, & Pedersen, 2006; Wojczynski, North, Pedersen, & Sullivan, 2007), demonstrating the high degree of comorbidity. Moreover, it appears that these populations display a three- to sixfold increased rate of mood disturbances overall (Arnold et al., 2006; Cole et al., 2006; Kato et al., 2006; Wojczynski et al., 2007). Research suggests that fibromyalgia and IBS are influenced by a combination of genetic factors, immune mechanisms, central nervous system abnormalities, neuroendocrine dysfunction, and environmental factors (Goldenberg, 2010), all of which may be dually implicated in depression and pain.

Nature of the Pain-Depression Relationship

Five prevailing hypotheses have been offered to address the timing and relationship of depression to that of chronic pain (Fishbain, Cutler, Rosomoff, & Rosomoff, 1997); these include the antecedent hypothesis, the consequence hypothesis, the scar hypothesis, the cognitive behavioral mediation hypothesis, and the independent hypothesis (Blackburn-Munro & Blackburn-Munro, 2001; Fishbain et al., 1997). Whereas the antecedent hypothesis suggests that depression precedes the development of pain, the consequence hypothesis views depression as a consequence resulting from the development of ongoing pain, whereby pain represents an increased risk factor for new onset of depression. Alternatively, the scar hypothesis proposes that, for some individuals, periods of depression preceding the onset of pain predispose to the emergence of a depressive episode following the onset of pain. The cognitive behavioral mediation model postulates that psychological mediators such as coping mechanisms mediate the bidirectional relationship between chronic pain and depression. The final hypothesis (independent hypothesis) suggests that the existence of shared pathogenetic mechanisms may underlie the relationship between comorbid pain and depression; however, these may also remain distinct diseases without causal interaction.

From their extensive review of the literature, Fishbain and colleagues concluded that the preponderance of the evidence has yielded support for the consequence hypothesis, suggesting that depression emerges as a consequence of chronic pain (Fishbain et al., 1997). Strong evidence in support of the scar hypothesis was also found in this review. Nevertheless, these data must be interpreted with caution, as results remain far from unequivocal and myriad other studies suggest that depression precedes the onset of pain. Nor are the aforementioned hypotheses necessarily mutually exclusive; individual variability is sufficient that there may be multiple routes to a depression-pain link.

The diathesis-stress model of the development of depression in chronic pain has similarly received substantial attention in the literature (Banks & Kerns, 1996). This model is in many respects in line with the scar-hypothesis, and the cognitive behavioral mediation model. The diathesis-stress model of the development of depression in chronic pain has been largely adapted from the depression literature and postulates that people have certain vulnerabilities or diatheses for developing depression. Diatheses may include biological, cognitive, and behavioral factors which, in the presence of stressful life events, may interact with one another so as to prompt the onset of depression. The amount or magnitude of environmental stress that is necessary to prompt the onset of depression depends on the extent of inherent vulnerabilities that an individual has (i.e., extensive vulnerabilities will be more sensitive to the effects of environmental stressors). Implicit in this model is the notion that behavioral and cognitive variables are important factors in the development of depression and that such factors can be largely negatively impacted by the presence of debilitating chronic pain (e.g., reduction of activities leading to reduced positive reinforcement leading to demoralization and then depression). Banks and Kerns have suggested that pain represents a viable stressor engendering aversive sensory and emotional sequelae, possible impairment and disability, secondary losses across various domains, and perceived nonvalidating responses from the medical system (Banks & Kerns, 1996). In conjunction with one another, these stressors may activate cognitive and/or behavioral diatheses, ultimately resulting in the development of depression.

The coprevalence of pain and depression is indisputable; yet the ambiguous nature of this relationship precludes determination of a single theory of causality. The hypotheses and models reviewed need not be deemed to be mutually exclusive; alternatively, each one may simply be applicable in different scenarios. The heterogeneity of the relationship between pain and depression and vice versa offers a compelling rationale for not treating patients with comorbid pain and depression as a homogenous entity. For a subset of patients, pain will be the primary concern, whereas for others depression may be the more salient and disabling complaint. Nevertheless, the clinical implication where comorbid depression and pain exist is clear: Irrespective of which condition is the primary concern, health-care providers ought to assess and treat both conditions so as to minimize patient suffering, optimize outcomes of each treatment, and curtail compounding health-care costs, which are exponentially increased in the presence of comorbid depression and pain. In addressing patient care, therefore, a determination of which affliction is the antecedent and which the consequent may be of limited clinical utility (Gureje, 2007).

Neurobiology of Pain and Depression

The gate-control theory of pain was introduced in the mid-1960s (Melzack & Casey, 1968; Melzack

& Wall, 1965) largely fueled by the absence of unified theories of pain that could adequately satisfy a comprehensive and validated explanation of pain. The gate-control theory offered a framework for understanding the pain experience beyond the assumption that pain is merely a product of tissue damage. That is, the gate-control theory improved upon the prevalent theories of the time (specificity theory and pattern theory) and introduced the then relatively novel notion that the brain (psychological processes) actively filters, selects, and modulates input, thereby influencing pain perception (Melzack, 2005; Melzack & Wall, 1965). In short, this theory posited that pain phenomena emerged following the modulation of sensory input by sensory feedback mechanisms and central nervous system influences (Melzack & Wall, 1965). Inherent in this theory was the idea that nociceptive input could be blocked at the level of the dorsal horn of the spinal cord. Further highlighting the multidimensional nature of pain, Melzack and Casey described pain along three dimensions: sensory-discriminative, motivational-affective, and cognitive-evaluative (Melzack & Casey, 1968). Thus, the gate-control theory proposed that the pain experience could be modulated by sensory dimensions *and* cognitive or psychological influences, inevitably establishing the role of psychological influences in treatment approaches to pain.

More recently, the neuromatrix model of pain emerged, describing a widely distributed network unique to each individual (Melzack, 1999). The body-self neuromatrix includes parallel somatosensory, limbic, and thalamocortical components that, alongside genetic influences, subserve the three dimensions of pain experience (sensory-discriminative, motivational-affective, and cognitive-evaluative) (Melzack, 1999, 2005). According to this model (and consistent with current perspectives on pain), the final pain experience is a product of the various dimensions of pain converging on the neuromatrix; the pain experience can thus be influenced by sensory, cognitive, and emotional inputs, intrinsic neural inhibitory modulation, and the body's stress-regulation systems (Melzack, 1999).

The biopsychosocial model builds on the gate-control and neuromatrix theories and recognizes psychological and social factors (in addition to biological factors) as central to a comprehensive understanding of pain. Interestingly, it appears that chronic pain and depression share a variety of underlying biological mechanisms that may serve to better explicate the high rates of comorbidity seen with chronic pain and depression. The most thoroughly studied biological influences, which have been proposed as viable explanations for the pain-depression relationship, include neurotransmission, immune and inflammatory mechanisms, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, and central nervous system abnormalities. Presented below is a brief overview of key findings from research concerning the role of neurotransmitters and other physiological processes in depression and pain since a more detailed review of the literature is beyond the scope of this chapter.

Neurotransmission

A basic understanding of the pain-modulating circuit is useful to appreciate neurotransmitter-mediated descending influences on pain perception. The pain-modulating circuit includes the amygdalae, the periaqueductal gray, the dorsolateral pontine tegmentum, and the rostral ventromedial medulla. This circuit exerts control over spinal and trigeminal dorsal horn nociceptors via descending pathways to ultimately result in analgesic responses (Fields, 2000). The brain areas comprising the pain-modulating circuit exert bidirectional influences on pain sensation via "on" cells, which facilitate nociceptive neurons, and "off" cells, which inhibit nociceptive neurons at the level of the dorsal horn (Fields, 2000). As hypothesized by Fields, this circuit represents an important link between pain and depression (or mood more broadly) through which mood can modulate pain perception (Fields, 2000).

Serotonin dysregulation is a theorized neural substrate of depression. Convergent lines of evidence have characterized the monoamine neurotransmitter serotonin (5-HT) as a modulator of pain perception, exerting descending inhibitory or descending facilitatory influences on spinal processing of nociceptive input. Serotonin, norepinephrine, and dopamine are primary neurotransmitters implicated in descending pain modulation pathways. The modulating effects of serotonin are undoubtedly complex and appear to vary widely according to pathology (for a detailed review see Bardin, 2011). Thus, serotonin can have either pronociceptive (e.g., peripheral serotonin potentiating the effects of inflammatory agents and therefore contributing to peripheral sensitization) or antinociceptive or analgesic effects depending on the receptor subtype and the site of binding. Empirical evidence suggests that following nerve injury, neuroplastic changes underlie enhanced facilitatory serotonin pathways,

which likely contribute to central sensitization and increased pain states (Bardin, 2011; Heinricher, Tavares, Leith, & Lumb, 2009). Conversely, in chronic inflammatory pain, it appears that serotonin exerts an inhibitory influence on pain by mediating endogenous mechanisms in the descending pain pathways. More specifically, research indicates that blockade of 5-HT_{1A} autoreceptors at the supraspinal level results in analgesic effects (Wei & Pertovaara, 2006). Effectively, blocking 5-HT_{1A} autoreceptors facilitates the release of 5-HT in descending pathways that exert inhibitory influences on pain. At the spinal level, activation of 5-HT_{1A} has yielded mixed evidence demonstrating facilitatory and inhibitory effects (Bardin, 2011). Data suggest that 5-HT_2 receptors in the spine and the periphery are implicated in sensitization of nociceptive processing, thus exerting pronociceptive effects (Bardin, 2011; Liu et al., 2005; Nakajima, Obata, Ito, Goto, & Saito, 2009; Wei, Chen, & Hong, 2005; Wu et al., 2001). These data indicate that 5-HT_2 receptor antagonists may have analgesic functions in the treatment of inflammatory and neuropathic pain. Whereas peripheral 5-HT_3 receptors have been found to enhance nociception, their role at the spinal level is currently less well-understood, but it appears that similar effects emerge in response to 5-HT_3 receptor activation (Bardin, 2011; Lang, Moalem-Taylor, Tracey, Bostock, & Grafe, 2006). Finally, spinal 5-HT_7 receptors are involved in indirect inhibitory influences on pain, suggesting that 5-HT_7 agonists may enhance the treatment of pain (Brenchat et al., 2010). Thus the more recent trends advocating for the use of antidepressants in the treatment of pain have emerged from this line of research and the consequent increasingly comprehensive appreciation for the complex role neurotransmitters play in pain perception and pain modulation.

Norepinephrine, another monoamine neurotransmitter, has also been implicated in depression and pain. It plays a major role in depression, and associations between the noradrenergic and serotonergic pathways have been well-established (Brunello et al., 2002; Werner & Covenas, 2010). With regard to pain modulation, norepinephrine has been shown to exert antinociceptive effects centrally via the activation of presynaptic α-2 adrenoreceptors on terminals of nociceptors or via activation postsynaptic α-3 adrenoreceptors, which consequently increase the release of inhibitory neurons (Benarroch, 2008; Pertovaara, 2006). Based on animal research models of pain, it has been proposed that low levels of norepinephrine may enhance nociception as a function of reduced inhibition of substance P (a neuropeptide prominently involved in nociception) release; nonetheless, the current research indicates that the long-term analgesic effect of activation of noradrenergic receptors is inconclusive, and research findings are often conflicting (Jasmin, Tien, Janni, & Ohara, 2003).

Immune and Inflammatory Mechanisms

Elevations of proinflammatory cytokines have been found in individuals suffering from depression as well as those with chronic pain. It has been proposed that cytokines released as part of the inflammation response may cause alteration in the metabolism of monoamines (Schrocksnadel, Wirleitner, Winkler, & Fuchs, 2006) and may activate C-reactive protein, which consequently leads to an increase of serum glucocorticoid levels and, over time, dysregulation of the HPA axis (Capuron, Ravaud, Miller, & Dantzer, 2004). Moreover, proinflammatory cytokines may originate in the peripheral and in the central nervous system and trigger short- and long-term effects that contribute to nociception and, in some cases, can lead to chronic hyperexcitability of nociceptors, altered phenotypic expression of nociceptors, abnormal pain processing, and exacerbation of noxious processes (de Oliveira, Sakata, Issy, Gerola, & Salomao, 2011; Ji & Neugebauer, 2007; Kim et al., 2007; R. J. Miller, Jung, Bhangoo, & White, 2009; Watkins & Maier, 2002). Various pain conditions—including complex regional pain syndrome, fibromyalgia, arthritis, and peripheral neuropathy—are associated with proinflammatory cytokine profiles (Omoigui, 2007; Uceyler, Rogausch, Toyka, & Sommer, 2007). Similarly, increased levels of proinflammatory cytokines are found in depression (Kim et al., 2007; Ovaskainen et al., 2009), thus yielding support for the role of immune and inflammatory mechanisms in altered pain processing and the emergence and maintenance of depressed mood.

Hypothalamic-Pituitary-Adrenal (HPA) Axis Dysregulation

The HPA axis is a major neuroendocrine system involved in controlling and directing reactions to stress as well as in the regulation of mood and other body processes. In a healthy, asymptomatic individual, several negative feedback loops regulate circulating cortisol levels (released as a product of HPA axis activation during the stress response). However, following chronic stress and consequently chronic

HPA axis activation, as in states of chronic pain and depression, the negative feedback loops appear to become dysregulated. HPA axis overactivation, characterized by increased cortisol activation and reduced suppression of morning cortisol levels, has been consistently found in individuals with depression (Dinan, 2001) and various chronic pain conditions (Clauw & Chrousos, 1997; Crofford et al., 2004; Korszun et al., 2002). In addition, immunological processes interact with HPA axis activity such that proinflammatory cytokines (implicated in depression and several chronic pain states as already mentioned) can contribute to abnormal HPA axis activity (Raison, Capuron, & Miller, 2006).

Taken together, these findings support the notion of common physiologic substrates underlying the link between the pathophysiologies of chronic pain and depression. These include shared neurobiological substrates that are consistent with the symptom presentation and the covariation-bidirectional nature of pain and depression. Consequently many of the current pharmacologic treatment approaches for pain and depression have been informed by the etiologic theories these convergent lines of research have stimulated.

Consequences of Comorbidity

The most detrimental potential risks associated with chronic pain include increased risk of suicidal ideation, attempted suicide, and suicide completion (Fishbain, 1999b). The rate of completed suicide has been estimated to be two to three times higher than the rate for the general population (Fishbain, Goldberg, Rosomoff, & Rosomoff, 1991). Recent estimates suggest that the national rate of suicide (all ages and both genders) is 11.8 per 100, 000 (McIntosh, 2011). Research has demonstrated that comorbid depression represents one of the risk factors for suicidality in chronic pain patients (Tang & Crane, 2006). Nevertheless, as highlighted by Tang and Crane, it is important to recognize that while comorbid depression is a predictor of suicide in some chronic pain patients, there are many chronic pain patients suffering from depression who do not endorse suicidal ideation or intent (Tang & Crane, 2006). Additional predictors of suicidality in chronic pain include family history of suicide, previous suicide attempt, being female, location and type of pain, high pain intensity, long pain duration, and the presence of comorbid insomnia (Tang & Crane, 2006). Consequently, clinicians working with individuals who suffer from pain, depression, or concurrent pain and depression should routinely evaluate for suicidality and closely monitor patients who endorse suicidal ideation or intent throughout the duration of treatment.

Given the astoundingly high estimated costs of chronic pain ($560 to $630 billion annually for direct and indirect costs), curtailing additional health care costs remains a priority. Research suggests that psychological distress, more specifically depression, predicts increased incidence rates of health-care utilization and health-care costs in some instances (Becker et al., 2010; Gameroff & Olfson, 2006; Katz & Yelin, 1993; Keeley et al., 2008; Toliver-Sokol, Murray, Wilson, Lewandowski, & Palermo, 2011); albeit in other instances it appears that the high service cost observed in patients with major depressive disorder and disabling pain appears to be a function of additive, not multiplicative costs of these two conditions (Arnow et al., 2009).

Finally, another noteworthy consequence where comorbid pain and depression occur is a poorer prognosis. Treatment and rehabilitation of people with chronic pain is complicated by the presence of depression and other psychiatric comorbidities (Gureje, 2007). For instance, disability level is negatively impacted by comorbid depression and pain, more so than in cases of depression without pain (Merikangas et al., 2003). A large-scale population study conducted across several European countries reported that the severity and duration of depression, the severity of insomnia, weight gain, psychomotor retardation, and concentration difficulties were significantly greater for individuals with comorbid major depression and chronic pain as opposed to those with major depression in the absence of chronic pain (Ohayon, 2004). Similarly, Geerlings and colleagues reported a decreased likelihood of remission of depressive symptoms mediated by the presence of chronic pain, thus contributing to an overall poorer prognosis (Geerlings, Twisk, Beekman, Deeg, & van Tilburg, 2002). Residual symptoms typically predict relapse of depression and are associated with a higher rate of suicide attempts (Judd et al., 1998; Keller, 2003; Kennedy & Foy, 2005; Sobocki, Ekman, Agren, Runeson, & Jonsson, 2006). Moreover, the prognosis for treatment of pain is adversely impacted as well. Patients with more severe depression derive fewer benefits from therapy intended to reduce pain (Jamison, Serraillier, & Michna, 2011) and complain of greater disability and interference with activity due to pain (Haythornthwaite, Sieber, & Kerns, 1991; Swimmer, Robinson, & Geisser, 1992). Additionally, chronic pain patients with comorbid

depression exhibit lower return-to-work rates compared with patients without psychiatric comorbidities (Demyttenaere et al., 2006; Fishbain, 1999a). Thus, convergent lines of research suggest that comorbid pain and depression are implicated in a worse treatment prognosis for pain and depression.

Treatment of Comorbid Pain and Depression

Exercise

Exercise therapy has been recommended for the treatment of mild to moderate depression and a variety of pain conditions, either as a first-line treatment approach or as adjuvant treatment alongside medications and/or psychotherapy. Results from randomized controlled trials (RCTs) have demonstrated that adherence to an exercise regimen in terms of approximately 150 minutes of moderate-intensity physical activity per week yields a favorable response rate comparable to that resulting from other treatments for mild to moderate depression, including medication and cognitive behavioral therapy interventions (Blumenthal et al., 1999; Carek, Laibstain, & Carek, 2011; Dunn, Trivedi, Kampert, Clark, & Chambliss, 2005). Remission and adherence rates to exercise interventions were found to be similar across groups (exercise, medication, and cognitive behavioral therapy) (Dunn et al., 2005). Aerobic exercise performed as part of a chronic pain rehabilitation program yields significant immediate and long-term benefits with regard to mood and perceived exertion (Sullivan, Covington, & Scheman, 2010), thus demonstrating that important treatment gains can be derived from participation in physical activities by individuals with comorbid pain and depression. Moreover, individuals with chronic pain frequently benefit from participating in different types of physical activity to preclude deconditioning of their muscles and further exacerbations of pain and disability. There is ample empirical support for mild strength training interventions for individuals with chronic widespread musculoskeletal pain (Brosseau et al., 2008; Busch, Barber, Overend, Peloso, & Schachter, 2007; Schneider, Vernon, Ko, Lawson, & Perera, 2009) and increasingly compelling evidence for the pain-reducing benefits of aerobic exercise in individuals with fibromyalgia (Hauser et al., 2010). Aerobic exercise appears to reduce pain and depression symptoms in patients with rheumatoid arthritis (Neuberger et al., 2007). Additionally, various types of exercise modalities have been recommended for patients with chronic low back pain (Sullivan, Scheman, Venesy, & Davin, 2012). Nonetheless, the literature lacks well-designed RCTs necessary to establish more definitive conclusions regarding the efficacy of specific interventions. Despite the absence of a consensus on specific physical activity guidelines and recommendations for individuals with chronic pain, it is generally agreed that different modalities of physical activity are typically beneficial in reducing pain and other important sequelae involved in the pain experience.

Cognitive-Behavioral Approaches

Psychotherapy has, for a very long time, been recognized as an accepted treatment approach for depression, albeit characterized by extensive variability among numerous therapeutic orientations. Nonetheless, it was not until relatively recently that psychotherapeutic interventions for the treatment of chronic pain became more widely accepted and used. Cognitive behavioral therapy (CBT) is a well-supported treatment approach for chronic pain. CBT interventions for chronic pain use psychological principles to elicit adaptive changes in the patient's behaviors, cognitions or evaluations, and emotions. Typically, the same core elements of CBT are found in CBT for psychiatric disorders and CBT for pain; these include patient education, self-monitoring, relaxation training, goal-setting and problem-solving skills, behavioral assignments (e.g., activity pacing, behavioral activation, physical activity) and cognitive restructuring, although the exact treatment components vary according to clinician and setting. Through cognitive restructuring exercises, patients become increasingly adept at recognizing the role of their emotions, cognitions, and interpretations in the modulation of their pain. The ultimate goal is recognition and reformulation of pessimistic, maladaptive thoughts in conjunction with the generation of balanced and adaptive alternative thoughts. Additional components frequently incorporated in a CBT intervention include social skills training, communication training, and broader approaches to stress management. These various treatment components are delivered within a supportive, empathetic, and collaborative patient-provider environment and can be delivered in the context of individual or group therapy.

Generally, cognitive behavioral therapists regard their role as that of a "teacher" or "coach." The goal in treatment is clearly stated as a collaborative effort that aims to augment the patient's self-management skills so as to improve daily function and quality of life rather than striving to completely eradicate

pain. Within this framework, patients are encouraged to regularly practice the skills they learn as part of treatment and consider themselves active participants of their pain rehabilitation or management program. Therapists foster the development of realistic, individualized goals to facilitate successful adherence to treatment and enhance the patient's pain management self-efficacy. Via a pain-oriented CBT intervention, many chronic pain patients benefit from improvements in their emotional and functional well-being and ultimately their global perceived health-related quality of life. Given the high rates of comorbidity of pain and depression, it is no surprise that CBT interventions for the treatment of a variety of pain conditions have frequently yielded positive results in aspects related to both pain and mood domains (Carson et al., 2006; Chou & Huffman, 2007; Eccleston, Williams, & Morley, 2009; Leibing, Pfingsten, Bartmann, Rueger, & Schuessler, 1999; Morley, Eccleston, & Williams, 1999; Turner, Mancl, & Aaron, 2006).

Specific improvements resulting from CBT interventions for chronic pain and its sequelae include measures of pain experience, mood/affect, cognitive coping and appraisal, pain behavior and activity level, and social role function when compared with wait list control conditions (Morley et al., 1999). When compared with other active treatments or control conditions, CBT has resulted in notable improvements albeit smaller effects (effect size ~.50), with regard to pain experience, cognitive coping and appraisal, and social role function (Morley et al., 1999). A more recent meta-analysis concluded that CBT has limited positive effects for pain disability, and mood, thus highlighting that there are insufficient data available to investigate the specific influence of treatment content on selected outcomes (Eccleston et al., 2009). Overall, it appears that mood improvements resulting from CBT remain robust at follow-up data points (Gardea, Gatchel, & Mishra, 2001). Nevertheless, critical considerations in evaluating the effectiveness of CBT for the management of chronic pain are centered on issues of effective delivery, lack of uniformity of treatment across settings, differences in delivery across clinicians and treatment populations, and variability in outcome variables of interest across research trials (McCracken & Turk, 2002). Compared with efficacy trials conducted under "ideal," tightly controlled conditions, effectiveness trials are more indicative of therapeutic effect under "real world" settings. Thus, effectiveness trials yield valuable information regarding the practical application of the therapeutic modality of interest. Currently, despite the existing efficacy trial–driven support for CBT, there is a dearth of effectiveness study trials for CBT for pain or CBT for pain and depression.

Acceptance-Based Approaches

Acceptance and commitment therapy (ACT) is the most common of the acceptance-based psychotherapies, often regarded as third-wave CBTs. ACT emphasizes the improvement of functioning for individuals by increasing psychological flexibility rather than strictly focusing on restructuring cognitions or targeting specific symptoms (Blackledge & Hayes, 2001; Hayes, Luoma, Bond, Masuda, & Lillis, 2006). In the context of chronic pain, ACT aims to reduce reliance on ineffective control strategies and experiential avoidance by fostering techniques that increase psychological flexibility. The six core processes underlying psychological flexibility as defined in ACT include acceptance, cognitive defusion, being present, self as context, values, and committed action (Hayes et al., 2006). Briefly, acceptance encourages chronic pain patients to actively embrace pain and its sequelae rather than attempting to change it, thus encouraging the patient to cease waging a futile fight directed at the eradication of pain. Cognitive defusion (deliteralization) techniques are employed to modify the function of thoughts rather than to reduce their frequency or restructure their content. In this manner cognitive defusion may simply alter the undesirable meaning or function of negative thoughts and thus decrease the attachment and subsequent emotional and behavioral response to such thoughts. The core process of being present emphasizes a nonjudgmental interaction between the self and private thoughts and events. Values are used as guides for electing behaviors and interpretations characterized by those values which an individual strives to instantiate in everyday life. Finally, through committed action, patients can realize behavior changes aligned with individual values. Thus ACT uses the six core principles in conjunction with one another to take a holistic approach toward increasing psychological flexibility and decreasing suffering. Patients are encouraged to view pain as inevitable and accept it in a nonjudgmental manner so that they can continue to derive meaning from life despite the presence of pain. The interrelated core processes exemplify mindfulness and acceptance processes and commitment and behavior change processes (Hayes et al., 2006).

Results of research on the effectiveness of ACT-based approaches for the management of chronic pain are promising albeit still warranting more rigorous evaluation (McCracken, Vowles, & Eccleston, 2005; Veehof, Oskam, Schreurs, & Bohlmeijer, 2011; Vowles & McCracken, 2008; Wetherell et al., 2011; Wicksell, Ahlqvist, Bring, Melin, & Olsson, 2008). Recent RCTs have reported significant improvements in pain catastrophizing, pain-related disability, life satisfaction, fear of movement, and psychological distress (Wicksell et al., 2008) as well as improvements for pain, depression, pain-related anxiety, disability, medical visits, work status, and physical performance (Vowles & McCracken, 2008). The most recent of these RCTs compared ACT and CBT treatments for individuals with chronic pain. The authors reported significant and comparable improvements for ACT and CBT treatments with regard to pain interference, depression, and pain-related anxiety (Wetherell et al., 2011). In general, current research indicates that acceptance-based therapies lead to favorable outcomes for patients with chronic pain, including improvements in mood. Specific improvements in pain-related anxiety, depression, and physical and psychosocial disability are significantly related to changes in psychological flexibility (Vowles & McCracken, 2008). Nonetheless, although promising in its early stages, the literature supporting ACT interventions is comparably smaller that that supporting CBT-based interventions for both depression and pain. Specifically, the American Psychiatric Association (APA, 2010) has designated ACT for pain as having "strong" research support and ACT for depression as having "modest" research support. These designations were made in accordance to the criteria for empirically validated treatments outlined by Chambless and colleagues (Chamblesss et al., 1998). There are currently no effectiveness trials investigating ACT for pain or ACT for pain and depression. Other acceptance-based interventions include contextual CBT and mindfulness-based cognitive therapy, although empirical research on the effectiveness of these therapies for the management of chronic pain is still in its infancy and insufficient to draw definitive conclusions.

Pharmacologic Approaches

A variety of antidepressants are now commonly incorporated into the treatment of pain disorders irrespective of the presence of comorbid depression. Agents acting on serotonin and norepinephrine have been shown to be efficacious treatment options for certain pain conditions; their beneficial effects are presumed to be a result of neurotransmitter-mediated pain modulation via ascending and descending neural pathways (as previously discussed in the neurobiology of pain section). Whereas randomized control trials evaluating the analgesic effects of selective serotonin reuptake inhibitors (SSRIs) have yielded mixed results (Moja, Cusi, Sterzi, & Canepari, 2005; Saarto & Wiffen, 2010; Urquhart, Hoving, Assendelft, Roland, & van Tulder, 2008), tricyclic antidepressants (TCAs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) have been shown to be efficacious in the treatment of some pain conditions, such as fibromyalgia and some types of neuropathic pain and have also been found to yield mood improvements (Arnold et al., 2004; Bradley, Barkin, Jerome, DeYoung, & Dodge, 2003; Detke, Lu, Goldstein, Hayes, & Demitrack, 2002; Fava, Mallinckrodt, Detke, Watkin, & Wohlreich, 2004; Hauser, Bernardy, Uceyler, & Sommer, 2009; Saarto & Wiffen, 2010). Nonetheless, these trials do not substantiate indiscriminate use of antidepressants for all pain conditions. For instance, a recent meta-analysis indicated that there is insufficient evidence to support the use of antidepressants for the treatment of arthritic pain (Richards, Whittle, & Buchbinder, 2011), and, despite sufficient evidence supporting the use of TCAs for chronic back pain, SSRIs are not a recommended treatment approach for chronic back pain (Chou et al., 2007). Meta-analytic reviews frequently cite the low quality of reporting in antidepressant trials as a major factor precluding researchers from arriving at more conclusive judgments regarding the efficacy of antidepressants for pain. It is also important to recognize that often several of the improvements reported are only minimally greater than those obtained with placebo, and the benefits begotten must always be carefully weighed against the adverse side-effect profiles of antidepressants (e.g., gastrointestinal distress, adrenergic effects, antihistaminic effects, anticholinergic effects, reduced sexual desire, lowered seizure threshold). Moreover, tricyclics have potentially lethal effects resulting from even a slight overdose. With regard to safety concerns, it is important to note that antidepressants have the potential to interact negatively with other drugs and with dietary supplements. Patients taking antidepressants should minimize

their consumption of alcohol. Alcohol can not only intensify symptoms of depression but can also affect an individual more strongly when he or she is taking antidepressants drugs; in larger amounts, it can increase liver strain. The presence of comorbid pain and depression results in a higher likelihood that the patient will be taking antidepressants in addition to other analgesic medications. Analgesic medications such as nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, anticonvulsants, or opiates present additional potential for a variety of side effects and safety concerns that must be taken into consideration irrespective of whether the patient is concomitantly taking antidepressants.

Clinical Guidelines for Practitioners

1. Assess both pain and depression.
   As pain and depression are highly comorbid conditions, it is essential to assess patients for symptoms of both chronic pain and depression in order to accurately conceptualize an individual case and to design the appropriate treatment intervention (Bair et al., 2003; Kroenke, 2005; Miller & Cano, 2009).
2. Evaluate functional impairment from both pain and depression.
   As part of the initial assessment, it is important to determine how impairing pain and/or depression are for various aspects of life such as work, school, relationships, and pleasurable activities (APA, 2010). In addition, it is recommended that health-care providers assess if depressive symptoms interfere with a patient's ability to follow medical protocols such as medication regimens and engaging in physical therapy exercises.
3. Treat both pain and depression.
   Treating not one but both pain and depression with empirically supported approaches such as CBT and exercise is highly recommended for most effective outcomes (Carson et al., 2006; Chou & Huffman, 2007; Eccleston et al., 2009; Leibing et al., 1999; Morley et al., 1999; Turner et al., 2006).
4. Enhance treatment adherence.
   Once treatment is initiated, it is recommended that adherence to self-management strategies be monitored carefully and that any potential barriers such as motivation, ongoing legal issues or economic or cultural barriers be addressed in order to enhance treatment effectiveness (APA, 2010; Nicholas et al., 2012).
5. Provide education to both the patient and the family regarding the interactions of pain and depression.
   If the patient gives permission, it can often be helpful to include family members in treatment in order to address questions and provide education regarding misperceptions about chronic pain and depression, medication protocols, and health behaviors such as exercise, sleep hygiene, nutrition, and substance use (APA, 2010).
6. Conduct risk assessments and interventions if needed for suicide risk.
   As one of the most detrimental possible risks of the comorbidity of chronic pain and depression involves increased risk of suicidal thoughts and actions (Fishbain, 1999b), it is necessary to assess for suicidal ideation and monitor and intervene if suicidal thoughts are present.
7. Coordinate patient's care with other health-care providers.
   It is recommended to have good communication with all members of the patient's health-care team in order to (a) provide comprehensive care, (b) prevent potential misperceptions regarding treatment protocols on the part of the patient, and (c) diminish the likelihood that a patient might mislead one member of the treatment team about the care or recommendations provided by another member of the treatment team (APA, 2010).
8. Guard against assuming that all patients experiencing pain and depression are similar.
   Pay attention to individual differences beyond the common presentations of pain and depression so as to customize treatment for better outcomes.
9. Remember that the psychological and emotional issues for pain and depression are very important.
   Normalizing and validating the emotional toll of pain and depression for each patient is part of the education process, and acknowledging emotional factors leads to better treatment planning.
10. Carefully assess and monitor patients regarding the side effects and possible toxic drug interactions of various medications.
    Even if they are not prescribing medications, health-care workers can provide valuable assessment and monitoring of both pain and depression medications and their possible

side effects as well as communicating that information to the health-care team (APA, 2010).

Summary

Having reviewed converging lines of evidence, this chapter demonstrates that chronic pain and depression are highly comorbid conditions commonly characterized by emotional and physical suffering and functional limitations. Research indicates that earlier episodes of depression are associated with an increased risk of developing various pain conditions and that depressed mood is associated with a reduced pain threshold and also increases multiple components of pain perception. Similarly, for some individuals, pain represents an increased risk factor for a new onset of depression. A definitive answer to the question of which condition is the antecedent and which is the consequence remains unclear. The various hypotheses and models reviewed may each be applicable in different scenarios, thus reflecting the inherent heterogeneity in the pain-depression relationship. For a subset of patients, pain will be the primary concern, whereas for others depression may be the more salient and disabling complaint; irrespective of which condition is the primary concern, both ought to be treated so as to minimize patient suffering and optimize outcomes of each treatment.

Chronic pain and depression share a variety of underlying biological mechanisms, which may account for the high rates of comorbidity of these two conditions. Biological substrates that serve as viable explanations for the pain-depression relationship include shared neurotransmitter pathways, immune and inflammatory mechanisms implicated in the emergence and maintenance of chronic pain and depressed mood, and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. Consequently many of the current pharmacologic treatment approaches for pain and depression, particularly with regard to antidepressant therapy for pain, have been informed by results emerging from this line of research. Exercise therapy is recommended for the treatment of mild to moderate depression and for a variety of pain conditions, as are evidence-based psychotherapeutic approaches. Various antidepressants have been shown to be beneficial in the treatment of certain pain conditions, particularly tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors. Various rigorous clinical trials have demonstrated that psychological interventions, particularly CBT interventions, are effective treatments for depression and pain, yielding improvements with regard to aspects of pain and mood domains. It is important to recognize that there is a vast amount of overlap within these therapeutic approaches. Commonly, patients with comorbid pain and depression are treated from a multimodal perspective, such that they may simultaneously be treated with pharmacologic agents and psychosocial therapeutic approaches.

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CHAPTER

21 Obesity

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Abstract

Cross-sectional and longitudinal studies indicate a positive association between obesity and depression. While some evidence suggests that depression is a risk factor for obesity, other findings indicate that obesity is a risk factor for depression. Therefore the directionality of this relationship remains unclear. Alternatively, there may be common mediating biological or environmental contributors accounting for this association. Potential biological mediators include dysregulation of the HPA axis, leptin resistance, and inflammatory immune responses. Environmental and psychological mediators may include a history of abuse and binge eating. It is also possible that the association between obesity and depression is most pronounced among particular subsets of individuals (e.g., women, those with more severe obesity). A better understanding of this depression-obesity association is needed to guide treatment recommendations for obese clients with comorbid depression. Future research is also needed to determine who is most vulnerable to experiencing comorbid depression and obesity.

Key Words: obesity, depression, comorbid depression, treatment recommendations

Introduction

Definition and Measurement of Obesity

There are several methods for determining a person's weight status and associated risk for weight-related medical conditions. However, body mass index (BMI) is the most commonly used measure for establishing weight status in epidemiological surveys as well as clinical assessments of individuals (NHLBI, 1998). BMI is calculated by dividing one's weight (in kilograms) by one's height (in meters) squared (i.e., BMI = kg/m^2). Table 21.1 summarizes BMI values associated with different weight categories. As illustrated in the table, overweight status is defined as a BMI of 25 to 29.9 kg/m^2, while obesity is defined as a BMI ≥ 30 kg/m^2. For instance, an individual who weighs 85 kg (187 lb) and is 1.6 meters (63 inches) tall would have a BMI of 33 kg/m^2, placing this person in the obese range.

In addition to BMI, waist circumference is another valuable weight metric, since excess abdominal fat is an important risk factor for disease. In particular, men with a waist circumference greater than 40 inches and women with a waist circumference greater than 35 inches are at increased risk for a variety of illnesses (NHLBI, 1998). Although used less often in research studies and clinical practice than BMI and waist circumference, dual energy x-ray absorptiometry (DXA) is a more accurate method of assessing body composition. DXA scans provide estimates of bone mass, fat mass, and lean mass for the full body and/or specific regions of the body (Ellis, 2000). While DXA assessment is not practical in many settings, some large-scale epidemiologic studies, such as the National Health and Nutrition Examination Survey (NHANES; http://www.cdc.gov/nchs/nhanes.htm) and the Coronary Artery Risk Development in Young

Table 21.1 Body Mass Index (BMI) Classification System

Weight Status	BMI
Underweight	<18.5 kg/m^2
Normal weight	18.5–24.9 kg/m^2
Overweight	25.0–29.9 kg/m^2
Obesity (class 1)	30.0–34.9 kg/m^2
Obesity (class 2)	35.0–39.9 kg/m^2
Extreme obesity (class 3)	≥40 kg/m^2

Adults (CARDIA; http://www.cardia.dopm.uab.edu/) study have begun to assess body composition using this technique.

Prevalence of Obesity

Recent epidemiologic data indicate that the prevalence of overweight (i.e., BMI ≥ 25 kg/m^2) among U.S. adults is 68% and the prevalence of obesity (i.e., BMI ≥ 30 kg/m^2) is nearly 34% (Flegal, Carroll, Ogden, & Curtin, 2010). Relative to Caucasians, rates of overweight and obesity are even higher among African Americans and Hispanics. For instance, 33% of white women are obese, compared with approximately 50% of black women (Flegal et al., 2010). Other risk factors for excess weight include lower income, less education, and older age (Flegal et al., 2010; Valdez & Williamson, 2002). It is also worth noting that the recent prevalence of excess weight among U.S. children and adolescents was approximately 17%, which represents a significant increase in recent years (Ogden, Carroll, Curtin, McDowell, Tabak, & Flegal, 2006).

Consequences of Obesity

There are a number of chronic and costly medical conditions associated with excess body weight. Overweight and obese individuals are at increased risk of hypertension, high cholesterol, type 2 diabetes, stroke, osteoarthritis, certain types of cancers, and sleep apnea (Field, Barnoya, & Colditz, 2002; NHLBI, 1998). Higher BMI is associated with diminished physical functioning and reduced quality of life as well (Coakley, Kawachi, Manson, Speizer, Willet, & Colditz, 1998; Fine et al., 1999). Obesity (but not overweight) is related to increased overall mortality; this association is primarily due to deaths from cardiovascular disease, certain types of cancers, and diabetes/kidney diseases (Flegal, Graubard, Williamson, & Gail, 2007). Not surprisingly, health-care expenditures are significantly higher among overweight and obese individuals (Bell, Zimmerman, Arterburn, & Maciejewski, 2011). In fact, annual obesity-related health-care costs in the United States were $86 billion based on 2006 figures (Finkelstein, Trogdon, Cohen, & Dietz, 2009). At the individual level, this corresponded to $1,429 more in annual medical spending for obese patients as compared with normal-weight patients (Finkelstein et al., 2009). Indirect costs associated with obesity (e.g., lost work productivity) are substantial as well (Wolf & Colditz, 1998).

While there are numerous studies associating obesity with a variety of "physical" health problems, much less research has been conducted to explore the relationship between obesity and psychiatric illness, including depression. Fortunately this situation is changing with growing interest in the link between depression and obesity, and there are intriguing recent findings that shed light on this important issue. Continued investigation of the relationship between obesity and depression is particularly warranted given the high prevalence rates of each condition as well as the suffering and diminished quality of life associated with both.

Relationship Between Depression and Obesity

Early Research Findings

Some of the initial research examining the relationship between obesity and depression concluded that obesity may actually be protective against depression. Termed the "jolly fat" hypothesis, Crisp and colleagues (Crisp & McGuiness, 1976; Crisp, Queenan, Sittampaln, & Harris, 1980) reported that obese men demonstrated significantly lower levels of depressive symptoms as compared to normal-weight men. A similar but nonsignificant pattern was observed in women as well (Crisp & McGuiness, 1976). Later findings also supported the "jolly fat" hypothesis among men but not women (Palinkas, Wingard, & Barrett-Connor, 1996). To explain this inverse association between weight status and depression among men, it was proposed that increased intake of certain nutrients, carbohydrates in particular, results in weight gain but decreased depressive symptoms through serotonergic activity (Palinkas et al., 1996).

Earlier studies examining the obesity-depression link included a number of methodologic limitations (Friedman & Brownell, 1995). First, there was tremendous variability in the assessment methods

employed for measuring psychopathology, and these measures of psychopathology generally were not sophisticated or well-validated. Early samples were relatively homogeneous and were not representative of more diverse segments of the larger population. Finally, the statistical approaches used in these early studies did not consistently account for covariates, such as age and gender, in examining the relationship between obesity and depression. Friedman and Brownell (1995) suggested that such limitations may have masked or misrepresented the obesity-depression relationship in early studies.

More recent work has begun to address some of these prior shortcomings. Recent studies have included clinical and nonclinical samples as well as more diverse samples in terms of race/ethnicity, education, and other important characteristics. Contemporary investigations more commonly use validated measures of psychopathology, including structured interviews establishing diagnostic criteria for depression, rather than symptom severity checklists or other screening instruments. In contrast to earlier studies, findings from more recent research often indicate a significant positive association between excess weight and depression; these findings are summarized in the following sections.

Current Estimates of Comorbidity

Simon and colleagues (2006) observed modestly increased rates of major depression among obese adults as compared with those who were not obese (18.6% vs. 16.0% for lifetime prevalence; 7.2% vs. 6.6% for 12-month prevalence). In another study, the lifetime prevalence of major depression was approximately 16%, 20%, and 28% for normal weight, obese, and extremely obese individuals, respectively (Petry, Barry, Pietrzak, & Wagner, 2008). Framed in a different way, Strine et al. (2008) found that adults with current or past depression were more likely to be obese than individuals without this psychiatric history. While 35% of currently depressed adults were obese, approximately 23% of individuals who were not currently depressed were obese. Similarly, 33% of individuals with a lifetime diagnosis of depression were obese, while 23% of individuals who had never been diagnosed with depression were obese (Strine et al., 2008).

Using a large nationally representative sample, Zhao and colleagues (2009) reported that rates of current and lifetime depression generally increase linearly as BMI increases, particularly among women. In another study using data from the same sample, Zhao et al. (2011) found that waist circumference was associated with increased risk of major depressive symptoms and moderate to severe depressive symptoms among overweight and obese women and men. Barry, Pietrzak, and Petry (2008) as well as Petry et al. (2008) reported that obesity was associated with increased risk of lifetime and past-year major depressive disorder and dysthymic disorder for women and men, while being overweight did not confer the same risk. Finally, Ma and Xiao (2010) found that, beginning at a BMI of 30 kg/m^2, relative weight was associated with the probability of moderate/severe depressive symptoms and major depression in a nationally representative sample of U.S. women. Women with class 3 obesity (BMI $\geq$ 40 kg/m^2) were at particularly high risk compared with those with class 1 obesity (BMI 30 to 35 kg/m^2). Furthermore, larger waist circumference was associated with more depressive symptoms independent of BMI.

Of course the prevalence of depression as well as other types of psychopathology is higher among individuals seeking treatment for weight loss as compared with those not seeking treatment (Fitzgibbon, Stolley, & Kirschenbaum, 1993; Prather & Williamson, 1988). In a review of studies including clinical weight loss samples, rates of depression were estimated to be 32% among individuals seeking treatment for obesity (McElroy, Kotwal, Malhotra, Nelson, Keck, & Nemeroff, 2004).

Sociodemographic Moderators

As mentioned already, there are several indications that the association between obesity and depression varies between men and women. Including a representative population-based sample of adults, Carpenter, Hasin, Allison, and Faith (2000) reported that obese women had an increased risk of depression as compared with normal-weight women. More specifically, obesity was associated with a 37% increase in the probability of having major depressive disorder. In contrast, obese men demonstrated decreased risk for major depression as compared with normal-weight men. Heo and colleagues (2006) as well as Onyike and colleagues (2003) also observed gender differences in the relationship between obesity and depressive symptoms. Women with higher BMI were at increased risk of experiencing recent depressed mood, although this association was not present for men. Friedman and Brownell (1995) indicated that women suffer from greater stigma for being overweight or obese, and this could help explain the gender difference. However, some

have suggested this gender difference may be attenuated when more severe levels of obesity are present (Dong, Sanchez, & Price, 2004).

Some studies have indicated that the association between obesity and depression may vary by race/ethnicity or education level. For instance, Simon et al. (2006) reported that this association was only significant among non-Hispanic whites and those with higher educational attainment. In another sample, the weight-depression association was strongest among Hispanic individuals (Heo et al., 2006). Thus, the moderating influences of ethnicity and education are less clear, but it seems that sociodemographic factors may be important covariates in understanding the magnitude of the relationship between weight and depression.

Other Potential Moderators of Comorbidity

In addition to sociodemographic factors, there are several environmental, behavioral, affective, and other relevant variables that may moderate the relationship between obesity and depression. For instance, Stunkard, Faith, and Allison (2003) have suggested that the emergence of the obesity-depression association could be conditional upon the severity of both illnesses. In other words, this association may be most likely among those who are more depressed and/or those who are more obese. In contrast, this association may be less pronounced with subclinical levels of depression or less severe levels of excess weight.

The subtype of major depressive episode experienced may also impact the likelihood of comorbid obesity. For instance, patients experiencing "atypical" features of depression—which includes symptoms of increased appetite, weight gain, hypersomnia, and psychomotor retardation—demonstrated significantly higher BMI than patients suffering from a more "typical" depression presentation (Kendler, Eaves, Walters, Neale, Heath, & Kessler, 1996; Sullivan, Prescott, & Kendler, 2002). Nearly 29% of women with atypical depression were obese compared with 3% to 6% of women with typical depression (Kendler et al., 1996). Similarly, Hasler et al. (2004) found that atypical depressive subtypes were associated with being overweight, while major depression more generally was unrelated to weight status.

Proposed Causes and Directionality of Relationship

Alternative theoretical models as well as empirical investigations have yielded different accounts to explain the direction and meaning of the relationship between depression and obesity. While some studies suggest that depression leads to obesity, others have concluded that obesity leads to depression. There is also a diverse field of research exploring a variety of underlying biological and environmental contributors that could account for the co-occurrence of obesity and depression. Models illustrating these potential relationships are included in Figures 21.1 and 21.2, and the evidence supporting these alternative explanations is summarized in the subsequent sections.

Depression as a Risk Factor for Obesity

Several of the symptoms associated with depression could contribute to the development or exacerbation of obesity. In particular, increased appetite and decreased activity are symptoms of depression that can have direct effects on weight. One study found that obese women who were depressed engaged in less physical activity and had a greater daily caloric intake as compared with obese, nondepressed women (Simon et al., 2008). However, this was not a longitudinal study and directionality could not be established. Sleep disruption is another common symptom of depression, and inadequate sleep has been implicated as a risk factor for obesity as well (Gangwisch, Malaspina, Boden-Albala, & Heymsfield, 2005).

In addition to the potential impact of depressive symptoms, the pharmacologic treatment of depression can also affect weight status. Some medications used in the treatment of depression, including tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs), commonly cause weight gain (Devlin, Yanovski, & Wilson, 2000; Zimmermann, Kraus, Himmerich, Schuld, & Pollmacher, 2003). However, the development of selective serotonin reuptake inhibitors (SSRIs) has reduced this concern, as these medications do not appear to have the same weight-altering properties as older agents (Devlin et al., 2000; Zimmermann et al., 2003). In fact, some evidence suggests that particular SSRIs may be associated with weight loss during the initial phases of treatment, although the weight effects with long-term therapy are less encouraging (Zimmermann et al., 2003).

Some longitudinal studies suggest that depressive symptoms may precede obesity or increase the risk of subsequent weight gain. Among individuals followed over time, depressive symptoms in childhood and adolescence were associated with obesity in early adulthood (Pine, Cohen, Brook, & Coplan, 1997; Vamosi, Heitmann, & Kyvik, 2010), although this

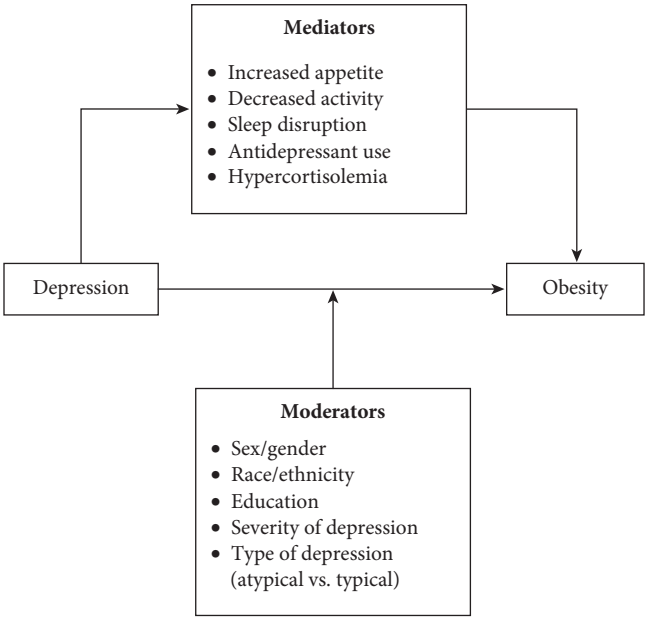

Figure 21.1 Proposed moderators and mediators of depression as a risk factor for obesity.

association is more pronounced in females and may be attenuated after accounting for relevant covariates (Pine et al., 1997). In one study, childhood depression was associated with a twofold increase in the risk of being overweight as an adult, and this association persisted after controlling for potential confounders (Pine, Goldstein, Wolk, & Weissman, 2001). Similarly, Goodman and Whitaker (2002) reported that depressed mood predicted obesity risk one year later among adolescents. In fact, baseline depression was predictive of the development of obesity among adolescents who were not previously obese as well as the worsening of obesity among those who were already obese at baseline. In another study examining a British birth cohort, women with adolescent-onset symptoms of depression had lower average BMI at age 15 compared with women with no symptoms of depression, but they experienced a faster rate of increase in BMI across adulthood and had higher BMI than their nondepressed peers

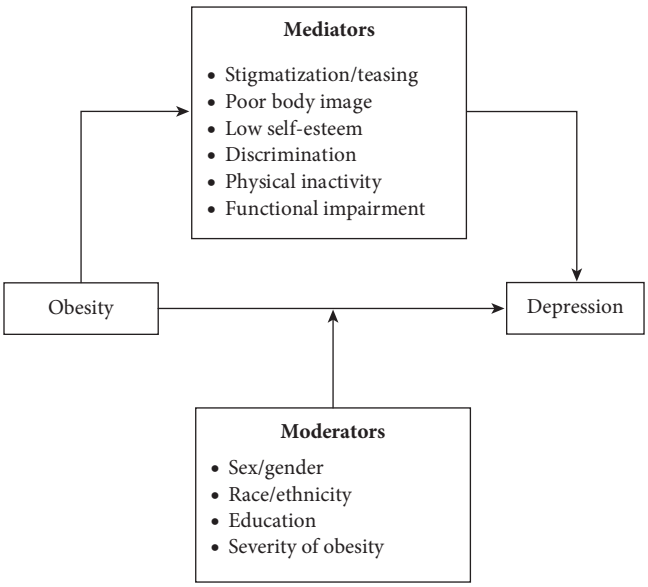

Figure 21.2 Proposed moderators and mediators of obesity as a risk factor for depression.

at age 53 (Gaysina, Hotopf, Richards, Colman, Kuh, & Hardy, 2011). In contrast, men with adolescent-onset symptoms of depression had lower average BMI at all ages.

Obesity as a Risk Factor for Depression

An alternative explanation of this relationship is that obesity serves as a predisposing risk factor for depression, and a few longitudinal studies have supported this conclusion. Among middle-aged and older adults, risk of depression at one- to five-year follow-up was greater for individuals who were obese at previous assessments (Roberts, Kaplan, Shema, & Strawbridge, 2000; Roberts, Strawbridge, Deleger, & Kaplan, 2002), although these results have varied depending on the measures employed within studies (Roberts et al., 2000). This prospective association may also be strongest among obese individuals who are not initially depressed (Roberts et al., 2002). In a subsequent study, obesity was associated with increased risk of depression five years later (Roberts, Deleger, Strawbridge, & Kaplan, 2003). In fact, baseline obesity doubled the risk of experiencing depression at follow-up (Roberts et al., 2003).

Another way of examining this relationship longitudinally is to measure changes in depressive symptoms following weight loss. Dixon, Dixon, and O'Brien (2003) studied changes in depression scores following bariatric surgery and found that weight loss was associated with significant postsurgical reductions in depression. These authors offered this as support for the notion that obesity (particularly more severe levels of obesity) may cause or exacerbate depression (Dixon et al., 2003). In addition to surgical interventions, behavioral treatments for weight loss also improve depressive symptoms. Wadden and colleagues (Wadden, Stunkard, & Liebschutz, 1988; Wadden et al., 1997) observed significant reductions in depressive symptoms during and after participation in behavioral therapy for weight loss. While these intervention studies suggest that weight loss may result in reduced depression, further investigation is needed to explore alternative causal explanations of these findings.

There are several potential explanations for why obesity results in increased risk for depression and, conversely, why weight loss could improve depressive symptoms. For example, many obese individuals experience social stigmatization that may result in shame, guilt, diminished self-esteem, and greater body dissatisfaction, which then leads to depressed mood (Friedman & Brownell, 1995; Ross, 1994). In fact, it is well established that obese individuals are subjected to a variety of negative attitudes and behaviors from others, including discrimination in educational, occupational, health-care, and family settings (Puhl & Brownell, 2003). This weight-related stigmatization is associated with more mental health symptoms, greater body image dissatisfaction, and lower self-esteem (Myers & Rosen, 1999). Thompson, Coovert, Richards, Johnson, and Cattarin (1995) found that obese children were subjected to weight-related teasing from their peers, which in turn led to increased body dissatisfaction and depressive symptoms three years later.

An alternative explanation for the linkage between obesity and subsequent depression deals with the activity levels and functional limitations of obese individuals. Since lower levels of activity are related to obesity (Lakerveld et al., 2011; Waller, Kaprio, & Kujala, 2008) and increased levels of physical activity are associated with fewer depressive symptoms (Brown, Ford, Burton, Marshall, & Dobson, 2005), it is possible that decreased activity helps to explain why obesity would be predictive of depression. In addition to limited levels of physical activity, obesity may be associated with decreased access to social activities and other rewards, serving as another potential risk factor for depression. Similarly, obese individuals have greater levels of functional impairment (Heo, Pietrobelli, Wang, Heymsfield, & Faith, 2010), which could also impact mood.

Studies Examining Bidirectionality

Although longitudinal studies examining the association between depression and obesity have become more common, few studies have simultaneously examined pathways from depression to obesity and from obesity to depression. Further, these few studies have produced conflicting findings. First, a study of adolescents found that symptoms of depression predicted obesity one year later, whereas obesity at baseline did not predict symptoms of depression at follow-up (Goodman & Whitaker, 2002). Similarly, a recent study examining trajectories of change in obesity and depression over a 15-year period during the transition from early to middle adulthood found that respondents who started out with higher levels of depressive symptoms experienced a faster rate of increase in BMI and waist circumference over time compared to those who had lower initial levels of depressive symptomatology; yet initial BMI and waist circumference were not associated with the rate of change in depressive symptoms over time (Needham, Epel,

Adler, & Kiefe, 2010). Finally, in contrast to these results, a study of older adults found that obesity at baseline was associated with an increased risk of major depression five years later; but baseline depression was not associated with an increased risk of obesity (Roberts et al., 2003). Clearly, further research is needed to clarify these conflicting findings.

Other Shared Environmental or Biological Contributors

A third explanation of the association between depression and obesity is that these conditions co-occur due to shared environmental, psychological, or biological causes. For instance, both conditions are associated with chronic physical illness, which could account for the co-occurrence of these conditions. In one study, the association between weight and depression was no longer significant after accounting for participants' physical health status, suggesting that poor health may mediate the relationship between obesity and depression (Jorm, Korten, Christensen, Jacomb, Rodgers, & Parslow, 2003). However, this hypothesis has not always been supported (Dong et al., 2004).

Both conditions have also been associated with the presence of binge eating behaviors, which has been proposed as a possible mediator of the obesity-depression relationship (Stunkard et al., 2003). Rates of mood disorders, including major depression, are significantly greater among obese individuals with binge-eating symptoms as compared with obese individuals who do not binge (Yanovski, Nelson, Dubbert, & Spitzer, 1993). In this study, the prevalence of major depressive disorder was 51% and 14% among obese patients with and without binge eating disorder, respectively.

Chronic life stress has been implicated in the development of obesity, associated metabolic changes, and depression. Particularly traumatic stressors that have been linked to the risk of both depression and obesity include experiences of childhood neglect, physical abuse, and sexual abuse (Gustafson & Sarwer, 2004; Stunkard et al., 2003; Vamosi et al., 2010). This common risk factor of childhood abuse could play a role in the subsequent development of the depression-obesity comorbidity.

It also has been postulated that shifting social trends related to decreased levels of physical activity and increased social isolation could be partly responsible for the co-occurrence of these two conditions (Goodman & Whitaker, 2002). Goodman and Whitaker (2002) also suggested that lower socioeconomic status could be a common underlying risk factor for obesity and depression, given the limited resources and increased hardships experienced by those with less income and limited education.

Shared biological dysregulations could be responsible for the relationship between obesity and depression. In fact, several neuroendocrine abnormalities have been identified that are common to both conditions. Researchers have implicated hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis and excessive secretion of cortisol in the development of depression and obesity (Bornstein, Schuppenies, Wong, & Licinio, 2006). Similarly, the neurotransmitter systems for serotonin, norepinephrine, and dopamine also appear to be related to each condition (Bornstein et al., 2006). It may be noteworthy that certain medications—including those that enhance serotonin, norepinephrine, and dopamine functioning—have shown efficacy for treating depression as well as modest weight loss (Greenway et al., 2010).

Other intriguing areas of research pertain to the role of leptin as well as inflammatory immune responses in obesity and depression (Shelton & Miller, 2010). Adipose, or fat, tissue in the body and its accumulation of lipids produces biochemical markers responsible for inflammation. Immune system activation and inflammation has been associated with depression as well (Shelton & Miller, 2010), leading these authors to suggest this inflammation process may mediate the link between depression and obesity. While leptin has been previously implicated for its role in obesity, more recent studies have suggested that leptin insufficiency and/or resistance may contribute to depression as well (Davis, 2010; Lu, 2007). Leptin may influence several biological processes relevant to obesity and depression, including HPA axis functioning mentioned previously as well as dopamine reward pathways related to motivational and emotional states.

Although promising, studies of the biological mechanisms responsible for the development of depression and obesity have generally occurred in parallel (i.e., biological mediators of obesity have been studied separately from the role of these mediators for depression). Integration of these two lines of study is needed to truly understand how these mechanisms may contribute to the shared risk of depression and excess weight. As suggested by Bornstein et al. (2006), shared biological causes of these conditions do not necessarily mean identical mechanisms for both diseases. A more plausible

explanation is that these overlapping biological systems interact with each other and with environmental influences to increase the comorbidity of depression and obesity for some individuals.

Summary of Findings on Comorbidity

Research findings generally suggest that a positive association between obesity and depression exists. It remains unclear if there is a causal relationship between the two conditions, and if so, the directionality of this relationship. It is also possible that the association is attributable to other mediating factors. In a recent qualitative review, Faith and colleagues (2011) summarized prospective studies exploring causal links between obesity and depression. These authors concluded that more consistent results have been obtained to support the hypothesis that obesity predicts subsequent depression, while there is more limited support for the notion that depression predicts subsequent obesity. However, it was also noted that this field is fraught with variable methodologic approaches, including heterogeneous measures, different covariates included in analyses, and discrepant lengths of follow-up (Faith et al., 2011). In a recent meta-analysis, Luppino et al. (2010) similarly found that baseline levels of overweight and obesity were significant predictors of depression at follow-up. While the reciprocal depression-to-obesity link was also significant, baseline depression was not predictive of being overweight at follow-up.

Several other conclusions have emerged from the literature on depression and obesity. First, the preponderance of studies has suggested a moderating effect of gender on this relationship, such that the association is more pronounced and consistent among women than men. While depression may be related to both overweight and obesity among women, it appears that this association may only emerge among obese (but not overweight) men. Regardless of gender, some evidence suggests that the association between weight status and depression is most pronounced with increasing levels of obesity.

Another plausible conclusion is that the association between obesity and depression is present only for particular subsets of obese individuals (Faith et al., 2011; Friedman & Brownell, 1995), highlighting the need to identify specific characteristics or experiences that put some obese individuals at greater risk for depression. This conclusion would help explain the divergent findings that have been obtained on this topic. Another challenge to drawing firm conclusions is that these topics have traditionally represented two distinct lines of research, with one focused on obesity and the other focused on depression.

Other Related Conditions

DIABETES

As mentioned previously, excess weight is a significant risk factor for diabetes. Likewise, rates of depression are significantly elevated among individuals with diabetes compared to those without this condition (Anderson, Freedland, Clouse, & Lustman, 2001). Therefore it is worth describing these associations to explore possible interplay between weight, diabetes, and depression. A substantial body of literature on comorbidity between depression and diabetes has emerged over the past few decades. Since 2000, at least two comprehensive reviews (Cosgrove, Sargeant, & Griffin, 2008; Talbot et al., 2000) and five meta-analyses (Anderson et al., 2001; Knol et al., 2006; Mezuk, Eaton, Albrecht, & Golden, 2008; Nouwen et al., 2010; Renn et al., 2011) have been published. Similar to work on depression and obesity, the majority of early studies examining comorbidity between depression and diabetes were cross-sectional. Over time, though, researchers have become increasingly interested in using longitudinal data to explore the hypothesis that depression and diabetes are causally related (see Golden et al., 2008; Lustman & Clouse, 2007; Mezuk et al., 2008; Renn et al., 2011).

Type 2 diabetes is hypothesized to increase the risk of depression through psychosocial stress and biochemical changes. First, being diagnosed with a serious chronic illness is stressful and may lead to symptoms of depression. In addition, treatment of type 2 diabetes requires lifestyle modifications, such as changes in diet and physical activity, which may induce stress (Golden et al., 2008; Holt et al., 2009; Mezuk et al., 2008; Renn et al., 2011). Finally, biochemical changes, such as nervous system arousal, may increase the risk of depression in individuals with diabetes (Holt et al., 2009; Renn et al., 2011).

While there is reason to suspect that diabetes leads to depression, researchers have also speculated that depression leads to diabetes. Depression is hypothesized to increase the risk of developing type 2 diabetes through at least four mechanisms. These include dysregulation of the HPA axis (Cosgrove et al., 2008; Holt et al., 2009; Knol et al., 2006; Mezuk et al., 2008), chronic inflammation (Holt et al., 2009; Mezuk et al., 2008), central obesity (Cosgrove et al., 2008; Mezuk et al., 2008), and

health behaviors (Cosgrove et al., 2008; Mezuk et al., 2008; Renn et al., 2011).

The evidence provides support for both hypotheses and is suggestive of a bidirectional relationship between depression and diabetes (Golden et al., 2008; Mezuk et al., 2008; Renn et al., 2011). A recent meta-analysis found that people with type 2 diabetes have a 24% increased risk of developing depression compared with nondiabetic controls (Nouwen et al., 2010); a second meta-analysis concluded that diabetes was associated with a "modest" increase in risk for depression (Mezuk et al., 2008). Other meta-analyses reported that depressed adults have between a 25% and 60% increased risk of developing diabetes compared with nondepressed controls (Cosgrove et al., 2008; Knol et al., 2006; Mezuk et al., 2008).

With the exception of one longitudinal study that simultaneously examined pathways from diabetes to depression and from depression to diabetes (Golden et al., 2008), previous research on depression and diabetes has either considered whether respondents with diabetes are more likely than controls to become depressed *or* whether respondents with depression are more likely than controls to develop diabetes. Additional studies examining the bidirectionality hypothesis are needed. Another important direction for future research is to identify mediators and moderators of the association between depression and diabetes (Albers, Kruse, Giani, & Icks, 2011; Osborn et al., 2011). This work may facilitate the development of interventions to reduce both depression and diabetes.

Treatment Considerations

Given the association between obesity and depression, it is important to consider how this comorbidity influences the assessment and treatment of both conditions. The prevalence of depression is elevated among obese populations (Petry et al., 2008; Simon et al., 2006). This is particularly apparent among individuals with severe obesity (Petry et al., 2008) and those seeking treatment for weight loss (McElroy et al., 2004). Therefore it is very important that clinicians providing obesity treatment evaluate for depressive symptoms in this clinical population. Initial evaluation for depression as well as ongoing monitoring of these symptoms over the course of obesity treatment is advisable.

Traditionally, individuals with comorbid depression seeking treatment for weight loss have been excluded from weight loss trials and programs until their depression was addressed. The rationale for this decision was that the depressive symptoms would interfere with individuals' ability to adequately participate and succeed in the weight loss efforts. It could also be argued that the challenges and potential disappointments of obesity treatment (e.g., regular weighing, dietary self-monitoring, weight regain) could exacerbate a depressive episode. Therefore it may be appropriate to provide treatment or refer depressed individuals for treatment targeting their depressive symptoms before enrolling them in a weight loss program. In the presence of severe depression, evidence-based treatment guidelines clearly indicate the provision of immediate and intensive depression treatment, particularly when comorbid conditions such as suicidal ideation or substance abuse are present (American Psychiatric Association, 2010; Barlow, 2008; Gotlib & Hammen, 2009; Nathan & Gorman, 2007; Richards & Perri, 2010).

Supporting the notion that obesity treatment may not be appropriate or effective for depressed individuals, some studies found that the presence of depression negatively impacted outcomes in weight loss trials. For instance, women with depression demonstrated poorer weight loss outcomes as compared with women without depression in one study (Linde et al., 2004). However, depression status was not predictive of treatment response among men, again highlighting potential gender differences in these relationships. Higher levels of depressive symptoms also have been related to weight regain following previously successful weight loss maintenance (McGuire, Wing, Klem, Lang, & Hill, 1999), further highlighting the need to adequately address depressive symptoms in order to effectively promote successful weight management.

More recent findings have challenged the notion that weight loss treatments are less effective or inappropriate for patients with comorbid depression. In a cognitive-behavioral, group-based intervention for obese women, Ludman et al. (2010) found no significant difference in weight loss achieved by depressed women as compared with nondepressed women at six-month follow-up (3.8 vs. 4.3 kg, respectively) or 12-month follow-up (3.0 vs. 3.6 kg, respectively). In addition, major depression was not associated with program attendance, suggesting that the presence of comorbid depression does not negatively impact women's attempts at weight loss.

While research has explored the effect of comorbid depression on weight loss outcomes, fewer conclusions can be drawn regarding the effect of weight status on depression treatment. However, there is

emerging evidence that excess body weight may be associated with poorer treatment response to antidepressant medications among depressed patients (Kloiber et al., 2007; Uher et al., 2009). Also, the negative effects of obesity seem to be most relevant for dampening improvements in neurovegetative symptoms related to sleep and appetite (Uher et al., 2009).

There are additional treatment considerations for patients experiencing comorbid depression and obesity. It is important to understand whether treatment targeting one of these conditions influences the other condition, as well as whether changes in the two conditions are related to each other. As mentioned previously, depressive symptoms significantly improved following bariatric surgery (Dixon et al., 2003) and behavioral therapy for obesity (Wadden et al., 1988, 1997). While obesity treatment has beneficial effects on depression, less can be said about the effects of depression treatment on weight. Beyond the potential weight-altering effects of certain psychotropic medications, there is a lack of published research exploring whether cognitive-behavioral treatments for depression influence weight. Given the numerous and often complex health problems faced by patients with depression and obesity, many of these individuals may be prescribed a number of medications. Therefore it is also important that clinicians assess and monitor possible drug interactions and/or toxic drug combinations in these patients.

One novel investigation deserves mention, as it explored the concurrent treatment of depression and obesity. Linde et al. (2011) found that group-based behavioral treatment resulted in modest weight loss as well as improvements in depression for obese women with comorbid depression. In this randomized trial, researchers compared the effects of a behavioral weight loss program and a combined program of behavioral weight loss treatment and cognitive-behavioral therapy for depression. Importantly, there was no difference between the two treatments for changes in either outcome (Linde et al., 2011). Based on data from this same trial, Simon et al. (2010) reported that initial improvement in one outcome (i.e., depression) was associated with improvement in the other outcome (i.e., greater initial weight loss).

Clinical Recommendations

Based on the available literature, there are a few recommendations that seem warranted regarding the assessment and treatment of individuals with comorbid depression and obesity. Clearly, the assessment of personal and historical factors that may contribute to both conditions—such as binge eating, history of abuse or neglect, and social stigma and isolation—is important. Given the stronger association between weight and depression for women, this component of the evaluation may be particularly relevant for this group. Currently, it is difficult to draw firm conclusions on the most appropriate way to proceed with treatment in the presence of comorbid depression and obesity. Clinically, it is reasonable to suggest that individuals would benefit from treatment targeting their depression before proceeding with behavioral or surgical weight loss interventions; this may be especially applicable when patients are suffering from more severe depression. However, recent investigations have not always supported this conclusion (Ludman et al., 2010), and further study is needed. When psychotropic medications are used in the management of depression, it is imperative to monitor side effects, including weight gain due to pharmacotherapy. Carefully monitoring weight gain among patients who are already overweight or obese as well as those who have a history of obesity, unstable weight, or disordered eating behaviors and cognitions may be particularly warranted.

On a positive note, it is certainly possible that targeting either one of these conditions will result in improvements in the other condition. This is a reasonable assumption since there is research suggesting that depression leads to obesity as well as studies demonstrating that obesity leads to depression. This also makes sense clinically, since there is notable overlap in the components of behavioral therapy for both conditions, including self-monitoring of behaviors, mood, and cognitions; problem-solving skills training; bolstering of social support; increasing physical activity; and cognitive restructuring of maladaptive thinking. Given this overlap in cognitive-behavioral treatment for obesity and depression, future research may reveal modified or tailored interventions that incorporate components of treatment that effectively target both conditions. Indeed, initial findings in this area are promising (Linde et al., 2011).

Future Research Directions

Several lines of research need to be pursued in the future in order to enhance our understanding of the relationship between weight and depression. First, more prospective designs are needed to clarify the directionality of this relationship. Such studies should include objective measurement of weight status and validated clinical interviews to assess depression. Moving beyond the measurement

of height, weight, and BMI toward the inclusion of alternative methods to assess body composition and distribution of lean and fat mass may provide valuable insights, particularly given recent evidence that the location of excess body fat (i.e., abdominal obesity) may be more important for depression risk than overall obesity (Needham et al., 2010; Vogelzangs et al., 2010).

Future studies in this domain should advance methodologically beyond measuring the bivariate associations between obesity and depression. Research must include models testing potential biological, environmental, and psychological moderators and mediators of this relationship (Faith, Matz, & Jorge, 2002). Such designs may help identify common biological pathways or early life experiences that predispose individuals to develop both conditions, which have enormous clinical implications for the assessment and management of depression and obesity. This future research could also aid in the identification of specific subgroups of obese individuals who are at increased risk for depression, and this will be important for the potential prevention of psychopathology. It is also possible that the direction and/or magnitude of the association between depression and obesity may vary across the life course, which represents another important question for future research. Another vital area for future investigation involves identifying the most appropriate treatment approaches to manage these conditions when both are present. Currently, it is unclear if depression must be treated prior to weight loss treatment, or if depression treatment and weight management could be effectively implemented concurrently.

Conclusion

Obesity and depression are two prevalent conditions, and both are associated with a variety of adverse outcomes, including diminished quality of life and impaired functioning. Therefore understanding how these two conditions relate to each other is an important topic of inquiry. While early research indicated an inverse relationship between weight and depression (i.e., obesity was associated with decreased risk of depression), more recent empirical work suggests these two conditions are positively related. Both cross-sectional and longitudinal investigations have demonstrated that excess weight is associated with increased depressive symptoms and/or likelihood of major depressive disorder. Also, these findings have been reported with both epidemiologic and clinical samples of children, adolescents, and adults.

There is evidence supporting both directions of this association, with some studies suggesting depression is a risk factor for obesity, while other studies have implicated obesity as a risk factor for depression. Other interesting areas of research suggest there may be common underlying biological or environmental contributors that account for the association between depression and obesity. Some of the most promising biological mediators of this association involve dysregulation of the HPA axis, leptin resistance, and inflammatory immune responses. A history of abuse and binge eating behaviors are examples of environmental or behavioral factors that have been proposed as possible nonbiological mediators of this relationship.

In terms of treatment considerations, there are limited and perhaps conflicting recommendations on how to best proceed in the management of patients with comorbid depression and obesity. Traditionally these two conditions have been treated separately. In fact, the presence of depression has excluded many individuals from enrolling in obesity treatment protocols, since some studies suggest that comorbid depression reduces the efficacy of weight loss treatment. However, there is some recent indication that major depression does not negatively impact attendance or weight loss in obesity treatment. Additional work is needed to better understand the most effective and appropriate treatment approach for individuals suffering from comorbid depression and obesity.

In conclusion, it is likely that the relationship between depression and obesity is complex and that the strength and direction of this association may vary across individuals or subgroups. Therefore it is important to determine who is most vulnerable to this comorbidity and what puts certain individuals at greater risk. It is also imperative that researchers determine how the presence of depression impacts the course of obesity and vice versa. On a related topic, further information is needed on how to best treat these conditions (either independently or concurrently) with existing evidence-based protocols. Alternatively, the development of appropriate interventions that effectively manage both conditions may be warranted.

Future Directions

- Is there a causal relationship leading from depression to obesity or from obesity to depression?
- What biological and/or environmental/psychosocial factors are potentially responsible for the association between depression and obesity?

• What measurements of weight status and depressive symptoms are most appropriate for future investigations in examining this obesity-depression association?

• Can obesity and depression be effectively treated concurrently or should they be treated as separate conditions?

• How does treatment targeting obesity impact depressive symptoms? How does treatment targeting depression impact weight?

• Does the presence of diagnosed depression negatively impact treatment outcomes for patients engaged in weight loss treatment?

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CHAPTER

22 Sleep Disorders and Depression

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Abstract

Major depressive disorder (MDD) commonly occurs with several sleep disorders, including hypersomnia, breathing or limb-related sleep disturbances, and most notably chronic insomnia. A bidirectional relationship exists between sleep and mood problems, and both issues often warrant timely clinical management. However, there are several assessment- and treatment-related complexities that complicate the clinical management of such patients. For example, there are several overlapping symptoms for MDD and both insomnia and hypersomnia, and the two sleep conditions are both listed as possible symptoms in the diagnostic criteria for MDD. This has led to a well-documented problem of underrecognizing and undertreating these significant disorders in the context of MDD. Moreover, certain effective depression treatments can actually worsen the coexisting sleep disorder. Understanding and treating both disorders (i.e., MDD and the co-occurring sleep disorder) is imperative for effective clinical care. Almost all (i.e., up to 90%) of those with depression report sleep problems. This chapter provides an overview of the etiologic, assessment, and treatment issues inherent in this very large, highly prevalent group.

Key Words: insomnia, hypersomnia, sleep disorders, major depressive disorder, treatment issues

Introduction

There are several sleep problems that commonly occur alongside major depressive disorder (MDD), including hypersomnia (Khan, Gardner, Prescott, & Kendler, 2002; Parker, Malhi, Hadzi-Pavlovic, & Parker, 2006), sleep-disordered breathing (Wahner-Roedler et al., 2007), restless legs syndrome (Cuellar, Strumpf, & Ratcliffe, 2007) and chronic insomnia (Buysse, Reynolds, & Hauri, 1994; Coleman, Roffwarg, & Kennedy, 1982). Whereas these disorders commonly co-occur with MDD, both hypersomnia and insomnia are also symptoms included in the diagnostic criteria for MDD (American Psychiatric Association, 2000). The inclusion of insomnia and hypersomnia in the diagnostic criteria for MDD, as well as the overlapping daytime sequelae of insomnia and hypersomnia with MDD (e.g., fatigue, cognitive and mood complaints) have created diagnostic confusion and problems with underdiagnosis and undertreatment of these significant sleep problems. This chapter discusses nosologic and treatment issues related to the inclusion of an insomnia or hypersomnia syndrome within the diagnostic criteria for MDD, and also conceptualizations of comorbid sleep problems. The chapter also covers treatment implications related to these tricky nosologic issues as well as treatment recommendations. All of the sleep disorders mentioned above are reviewed in the context of MDD. Given that the greatest association between MDD and sleep problems is between insomnia and MDD, insomnia is the focus of the chapter.

Insomnia

Definition and Comorbidity

The diagnostic criteria for Primary Insomnia require that a sleep complaint (e.g., sleep onset or maintenance difficulties or nonrestorative sleep)

persist for a minimum of one month (American Psychiatric Association, 2000). There are no formal quantitative criteria for what constitutes sleep onset or maintenance difficulties. Whereas greater than or equal to 31 minutes on at least 3 nights per week for 6 months is one commonly cited suggested cutoff for chronic insomnia (Lichstein, Durrence, Taylor, Bush, & Riedel, 2003), others have provided evidence that no one cutoff provides optimal sensitivity and specificity (Lineberger, Carney, Edinger, & Means, 2006). Aside from a subjective sleep complaint, the diagnostic criteria require the presence of clinically significant distress or impairment in social, occupational, or other areas of functioning. This criterion generally includes one or more of the daytime symptoms of insomnia listed in the Research Diagnostic Criteria for Insomnia (Edinger et al., 2004), including fatigue/malaise, attention/concentration problems, negative mood, social/vocational dysfunction or poor school performance, somatic symptoms such as tension headaches and/or gastrointestinal symptoms in response to sleep loss, motivation/energy/initiative reduction, daytime sleepiness, and/or worry about sleep. Similarly, insomnia related to an Axis I disorder (e.g., MDD) includes the aforementioned criteria, but the insomnia (1) occurs within the context of another Axis I disorder and (2) is sufficiently severe to warrant independent clinical attention (American Psychiatric Association, 2000).

Subjective complaints of sleep disturbance are a prominent feature of MDD, as up to 90% of those with MDD complain of insomnia (Kupfer, Reynolds, Ulrich, Shaw, & Coble, 1982; Reynolds & Kupfer, 1987). In addition to subjective complaints, the sleep of those with depression often contains characteristic objective markers. A meta-analytic comparison of electroencephalographic (EEG) sleep indices of those with healthy sleep, insomnia only, and those with depression (N = 7,151), found that relative to healthy sleepers, those with MDD, and those with insomnia only had increased sleep onset latency as well as decreased sleep duration, sleep efficiency (i.e., the percentage of time asleep relative to the time spent in bed), duration of slow-wave sleep, and percentage of slow-wave sleep (Benca, Obermeyer, Thisted, & Gillin, 1992). Relative to healthy sleepers and those with insomnia only, those with depression often have a shortened latency to rapid-eye-movement (REM) sleep and increased REM sleep percentage. EEG coherence analyses have found reduced coherence (i.e., less similarity of activity in two cortical areas) in those with depression and that reduced coherence may predict depressive recurrence (Fulton, Armitage, & Rush, 2000). However these differences appear to be moderated by age and sex (i.e., they are most reliably found in female adolescents) (Armitage, Hoffmann, Emslie, Rintelmann, & Robert, 2006; Robert et al., 2006). Relative to those with healthy sleep, those with depression often have a lower ratio of slow-wave counts in the first non-REM (NREM) period relative to the second NREM period (Kupfer, Frank, McEachran, & Grochocinski, 1990). Given the connection between slow-wave sleep production and the homeostatic regulatory system, this may be regarded as evidence of possible homeostatic dysregulation in depression. Interestingly, a lower ratio is associated with poorer depression treatment outcomes and also depressive recurrence (Jindal et al., 2002; Kupfer et al., 1990; Thase, Fasiczka, Berman, Simons, & Reynolds, 1998).

The fact that no one marker has been found to have very high sensitivity and specificity, it is perhaps not surprising as the range of presentations of MDD is varied. MDD is a polythetic diagnosis; that is, because many symptoms comprise the DSM-IV-TR (American Psychiatric Association) diagnosis, some of which are antithetical (e.g., appetite loss versus appetite gain; psychomotor agitation versus retardation; insomnia versus hypersomnia), there are many combinations at clinical presentation. It may be unrealistic to expect that the sleep of one clinical manifestation of MDD, such as MDD with a seasonal pattern, would be the same as a different MDD presentation, such as MDD in combination with melancholia. Indeed, MDD may be better conceptualized as an umbrella term for unipolar depressions rather than a singular diagnosis per se.

Prevalence and Impact

Insomnia is a highly prevalent disorder affecting approximately 10% to 15% of the adult population (Ford & Kamerow, 1989; Morin, LeBlanc, Daley, Gregoire, & Merette, 2006; Ohayon, 2002), with approximately 30% of the population suffering from insomnia symptoms at any given moment (Morin et al., 2006). In the setting of depression treatment, up to 90% of those with MDD report sleep difficulties (Kupfer et al., 1982; Reynolds & Kupfer, 1987). Epidemiological studies have shown that 41% of depressed patients report sufficient insomnia symptoms to warrant an additional DSM-IV diagnosis of insomnia (Breslau, Roth, Rosenthal, & Andreski, 1996; Stewart et al., 2006).

In sleep treatment settings, those with comorbid MDD are the most commonly seen patient group (Edinger et al., 1989); in fact, on inclusion of those with comorbid depression, number of insomnia patients presenting for sleep treatment without another psychiatric disorder is almost doubled (Buysse, Reynolds, & Hauri, 1994; Coleman, Roffwarg, & Kennedy, 1982; Jacobs, Reynolds, Lovin, & Ehrenpreis, 1988).

Whereas the impact of insomnia was previously underrecognized, the considerable cost of this condition is now evident. Insomnia is associated with increased disability and health care utilization (Novak, Mucsi, Shapiro, Rethelyi, & Kopp, 2004; Ozminkowski, Wang, & Walsh, 2007; Roth et al., 2006; Stein, Belik, Jacobi, & Sareen, 2008). There are also staggering economic losses related to insomnia-related absenteeism and decreased work productivity (Daley, Morin, LeBlanc, Gregoire, & Savard, 2009). For example, Ozminkowski and colleagues (2007) examined the six-month burden in medical costs for adults with untreated insomnia versus those without; they reported that, on average, the direct and indirect costs for the former group were $1,253 greater than for those in the latter and $1,143 greater for the elderly with insomnia versus those without. The direct annual cost for those with untreated insomnia in a depressed population ($4,858) is higher than that for those with depression only ($4,007) (Asche, Joish, Camacho, & Drake, 2010). Aside from the economic burden of insomnia, this disorder is associated with overall reduced quality of life (Zammit, Weiner, Damato, Sillup, & McMillan, 1999) in addition to several daytime symptoms, which can lead to a vast array of interpersonal consequences. Similarly, those with depression can be perceived as hostile and/or submissive, which can disrupt their interpersonal needs and contribute to the maintenance of their depression (Constantino et al., 2012). Thus comorbid insomnia and depression have both economic and personal ramifications.

There are many ways in which insomnia impacts MDD negatively. Insomnia has been shown to predict MDD onset and exacerbate MDD symptoms (Ford & Kamerow, 1989; Judd et al., 1998; Perlis, Giles, Buysse, Tu, & Kupfer, 1997; Pigeon et al., 2008). Insomnia also complicates the management of MDD. The presence of significant insomnia predicts poorer response to empirically supported psychotherapies and pharmacotherapies (Buysse et al., 1999; Thase et al., 1997; Thase, Simons, & Reynolds III, 1996). Moreover, after successful treatment (i.e., remission) using empirically supported psychotherapies and pharmacotherapies, insomnia can remain as a clinically significant condition in a significant proportion of patients (Carney, Harris, Friedman, & Segal, 2011; Carney, Segal, Edinger, & Krystal, 2007; Manber et al., 2003; Nierenberg et al., 1999). Given the high prevalence of insomnia and MDD and the costs associated with these conditions, effective assessment and treatment for those with comorbid insomnia and MDD must be a high priority.

An additional socioeconomic cost of insomnia is the risk it confers for suicide. Suicide is a common cause of premature mortality, with the global rate of suicide estimated to be 14 to 16 per 100, 000 individuals, totaling a million deaths each year (Pigeon & Caine, 2010). Sleep difficulties have been recognized as a potentially important risk factor for suicidal thoughts and behaviors (Goldstein, Bridge, & Brent, 2008; Liu & Buysse, 2006; Singareddy & Balon, 2001; Wojnar et al., 2009). The most extensive literature surrounding sleep and suicide involves adolescents, in whom insomnia and other sleep disturbances have reliably been linked to an increased risk of suicidal ideation and behavior (Goldstein et al., 2008; Liu, 2004; Nrugham, Larsson, & Sund, 2008). In a large adolescent sample, those who obtained less than eight hours of sleep per night were three times more likely to attempt suicide, even after adjusting for depressive symptoms (Liu, 2004). More recently, Goldstein et al. (2008) reported a relationship between sleep disturbance and completed suicide among adolescents, with higher rates of sleep difficulties within the weeks preceding suicide. Thus insomnia may act as an important warning sign for suicide in this population.

A similar pattern exists for sleep and suicide in adult populations. In a national comorbidity survey, sleep disturbance in adults was consistently linked with suicidality, with problems of sleep onset having the strongest association with suicidal ideation, planning, and attempts (Wojnar et al., 2009). Among psychiatric inpatients, Hall and colleagues (1999) found that insomnia was among the most common symptoms prior to a serious suicide attempt. Likewise, in a sample of psychiatric outpatients, sleep problems were related to suicidal ideation even after controlling for severity of depressive symptoms (Bernert, Joiner, Cukrowicz, Schmidt, & Krakow, 2005) or the duration of the illness (Chellappa & Araujo, 2007). Severe insomnia at the time of diagnosis of

depression has been identified as one of the limited clinical predictors of completed suicide within the first year (Fawcett et al., 1990). Furthermore, suicidal thoughts are more common among those with those with insomnia and depression than those with depression only (Fawcett et al., 1990). Accordingly, clinical evaluation of sleep disorders among those with depression is imperative given its association with suicidality.

Conceptualizations of Comorbid Insomnia

Whereas previous conceptualizations of sleep in depression focused on sleep solely as a symptom that would presumably resolve with depression treatment, current conceptualizations recognize that insomnia more commonly occurs as a comorbid condition (National Institutes of Health State of the Science Conference Statement, 2005). Moreover, simplistic terms, such as *secondary insomnia*, imply that insomnia is a symptom of the primary illness (i.e., MDD) when in fact, the etiological and treatment-related significance of insomnia in those with MDD varies considerably (Lichstein, 2000). In Lichstein's (2000) conceptualization, there are a variety of ways in which insomnia and depression may be related. For some, insomnia may be a symptom, or an absolute secondary sleep problem caused by MDD. In such cases, the insomnia would be expected to resolve with depressive recovery. Indeed, insomnia may be successfully resolved in about half of patients whose depression was successfully treated (Carney, Segal, Edinger, & Krystal, 2007; Manber et al., 2008; Nierenberg et al., 1999); therefore there are probably some circumstances wherein this conceptualization is appropriate. Lichstein (2000) further suggests that the depression and insomnia relationship may be only partial, such that they may interact but while there may also be some independence. Unlike the case above, depressive recovery may be associated with sleep improvement but not necessarily full remission of insomnia. Studies of residual insomnia, such as those cited above, often test for statistically significant time effects for the insomnia symptom rather than the clinical significance of the improvement; therefore little is known about this possibility. An additional problem is that many depression trials examine sleep items from depression inventories rather than validated insomnia tools, and fatigue, a prominent insomnia symptom, is ignored or included in the depression score. One study examined sleep improvement on a validated sleep measure after depression treatment and found that most of the individuals studied still had clinically significant levels of sleep disturbance after recovering from a depressive episode recovery (Carney et al., 2011), suggesting that for many, recovery from depression may improve but not resolve sleep problems. These results may also lend some support to Lichstein's (2000) third category: that is the insomnia and depression relationship may be specious or that they may be independent conditions. Under this circumstance, treating depression (or insomnia) would have little effect on the other condition. In practical terms, practitioners are unlikely to be able to discern which of these categories applies to a particular patient. Disentangling, from the patient's history, whether the insomnia has caused or was caused by the depression may be made even more difficult owing to the deficits in autobiographical memory that are seen in depression (Williams & Scott, 1988). It may be parsimonious to treat disturbed sleep when the patient is complaining of significant sleep problems, to treat depression when there is depression, and to treat both when they co-occur. There are no noteworthy treatment implications for distinguishing between comorbid versus primary insomnias, as hypnotics and/or cognitive behavioral therapy for insomnia (CBT-I) are the recommended approaches to both types of insomnia (National Institutes of, 2005). This sentiment is echoed in the proposed criteria for DSM-5 (American Psychiatric Association, n.d.). The proposed revised criteria for insomnia in the DSM-5 will eliminate the distinctions between comorbid and primary insomnias altogether; instead, proposed criteria will focus on whether there is a significant insomnia complaint. Thus, although the precise nature of the relation between insomnia and depression for an individual patient may be unknown, it should be stressed that there is ample reason to conclude that insomnia is most often a comorbid condition that is worthy of clinical attention (Lichstein, 2000; National Institutes of Health State of the Science Conference Statement, 2005).

Etiology

To date, biological theories have focused on shared neurobiology pathways for sleep and depression. Such studies have stressed the presence of nocturnal EEG abnormalities in depressed patients,

such as REM latency and increased REM density and impaired sleep continuity (for review see Benca, Obermeyer, Thisted, & et al., 1992; Buysse & Kupfer, 1993) or abnormalities in the EEG spectra, such as decreased delta power and delta ratio (Armitage, 1995). The predominant neurochemical models have suggested that sleep disturbance in depression relates to cholinergic hypersensitivity (Gillin, Sitaram, & Duncan, 1979) and/or serotonergic or noradrenergic sensitivity (McCarley, 1982). Last, neuroimaging studies have reported metabolic abnormalities in the sleep-wake and emotion areas of the brain in depressed patients (e.g., Nofzinger et al., 2005). The etiological relationship between sleep and depression is not fully understood, as not every MDD patient manifests the purported biological sleep markers from EEG, neurochemical, or neuroimaging studies. In sum, the exact nature of the relation between insomnia and comorbid MDD (MDD-I) is unknown and may vary widely from patient-to-patient.

One useful way to conceptualize MDD-I cases is to consider that there are predisposing, precipitating, and perpetuating factors for the insomnia and to choose intervention strategies based on this case conceptualization. This model for chronic insomnia, first introduced by Spielman (1987), suggests that there may be predisposing factors for insomnia that, in the absence of a stressor, will not lead to symptoms of sufficient severity to be worthy of an insomnia diagnosis. Such predisposing factors may also be shared with depression (e.g., a neurochemical sensitivity, polygenetic predisposition, traits such as perfectionism, etc.). If a vulnerable person encountered a stressor/precipitating event, which could include endogenous or environmental occurrences, this could be sufficient to create insomnia worthy of a diagnosis. The sleep disorder may resolve when the stressor resolves; however, if compensatory behaviors occur in response to the sleep disturbance, these factors may become the perpetuating factors and lead to more chronic insomnia. Such factors may also supplant the original precipitating causal factors and become the foci of treatment targeting; in other words, what may initially cause the insomnia may not be what maintains it. For example, those with insomnia are more cognitively inflexible in their belief that they must exert effort to produce and compensate for sleep (Espie, Broomfield, MacMahon, Macphee, & Taylor, 2006). Those with insomnia also have more unrealistic sleep expectations, which purportedly set the stage for sleep-disruptive habits (Edinger, Fins, & Glenn, 2000; Morin, Stone, Trinkle, Mercer, & Remsberg, 1993). Studies in which such beliefs are successfully targeted have shown that belief change relates to other indices of sleep improvement (Carney & Edinger, 2006). Studies in those with MDD-I have shown that they manifest similar levels of unhelpful thinking about sleep as those with primary insomnia (Carney et al., 2010; Kohn & Espie, 2005). Furthermore, many patients with chronic insomnia develop conditioned arousal at bedtime through the repeated association of the bed and bedroom with unsuccessful sleep attempts (Bootzin & Epstein, 2000; Hauri, 2000). Even among individuals whose sleep disturbance initially represented an absolute secondary MDD symptom, the nightly experience of unsuccessful sleep attempts could result in conditioned arousal and subsequent attempts to make up for lost sleep by spending excessive time in bed each night or napping during the day (Edinger & Wohlgemuth, 1999; Morin, 1993; Spielman, Saskin, & Thorpy, 1987). These practices are associated with prolonged sleep difficulties because of the deleterious effects on homeostatic and circadian mechanisms that control the normal sleep/wake rhythm (Edinger & Wohlgemuth, 1999; Morin, 1993; Spielman et al., 1987). Thus sleep-disruptive cognitions and habits may play important perpetuating roles for insomnia in MDD patients and, in turn, may merit specific treatment attention (Smith, Huang, & Manber, 2005). Studies in those with depression have found sleep disruptive thoughts and behaviors similar to those seen in patients with MDD-I (Carney & Edinger, 2006; Kohn & Espie, 2005); thus the most proximal causal mechanisms may be shared across MDD and insomnia.

Thus, although insomnia in some could arise from the endogenous/neurophysiological disturbances described above, insomnia could also develop as an acute stress reaction to the onset of psychiatric illness. Depression could also develop as a stress reaction to chronic insomnia, or insomnia could result from sleep-disruptive behaviors common in depressed patients (e.g., spending increased time in bed, inactivity, worrying/ruminating in bed).

Assessment and Intervention Strategies

Several well-established methods are available for the assessment of insomnia, such as questionnaires, sleep diaries, actigraphy, and clinical interviews (Buysse, Ancoli-Israel, Edinger, Lichstein, & Morin, 2006). One commonly used self-report questionnaire is the Insomnia Severity Index (ISI) (Morin, 1993), which provides an index of the global

severity of insomnia by assessing the nature, severity, and impact of insomnia (Bastien, Vallieres, & Morin, 2001; Morin, Belleville, Belanger, & Ivers, 2011). This measure has been found to be valid and sensitive in detecting changes in self-reported sleep problems across treatment, as demonstrated by significantly lower ISI total scores at posttreatment relative to baseline (Bastien et al., 2001). Sleep diaries are the gold standard in the assessment of insomnia, as they provide detailed information about the severity and variability of sleep disturbance, sleep scheduling, and sleep-wake patterns (Buysse et al., 2006). The Consensus Sleep Diary (Carney et al., 2012) is a consensus-based tool designed by a panel of insomnia experts with input from patient groups; it is recommended for the prospective monitoring of sleep.

The clinical interview is another important part of assessment that can be supplemented by a structured, validated interview tool to assess for insomnia and other sleep disorders. For example, The Insomnia Interview Schedule (IIS) (Morin, 1993) is a semistructured interview that inquires about the nature and severity of the sleep difficulty; the current sleep-wake schedule; the onset, course, and duration of insomnia; and the history of hypnotic use. In addition, information is collected about health habits that influence sleep (e.g., alcohol consumption), environmental factors (e.g., bed partner), and sleep habits (e.g., watching television in bed), and other factors that influence sleep (e.g., stress). The Duke Structured Interview for Sleep Disorders (DSISD) (Edinger et al., 2004) is another semistructured diagnostic interview used to assist with sleep disorder diagnoses. The interview is designed to aid in determining sleep disorders in accordance with both the DSM-IV-TR and the International Classification of Sleep Disorders (ICSD-2) (American Sleep Disorders Association, 1996) sleep disorder nosologies. The clinical interview will provide important information and provide a fuller picture of the disorder, including the perpetuating factors, which will be important for later treatment targets.

In addition to these self-reported assessment tools, an actiwatch is a portable device, worn like a wristwatch, that provides an indirect but objective measure of sleep and wake activity via accelerometer measurement of movement (American Sleep Disorders Association, 1996; Ancoli-Israel et al., 2003; Lichstein et al., 2006; Littner et al., 2003; Sadeh & Acebo, 2002; Sadeh, Hauri, Kripke, & Lavie, 1995). An actigraph yields typical sleep-pattern estimates, including sleep onset latency, wakefulness after sleep onset, and total sleep time (Lichstein et al., 2006). Although not indicated for routine diagnosis, assessment of severity, or management of insomnia, an actigraph is a useful adjunctive tool in the assessment of insomnia (Buysse et al., 2006).

The most prominent complaint in insomnia is fatigue (Shapiro, 2004). An important distinction for clinicians to make is between fatigue and sleepiness, two terms often incorrectly used interchangeably. Sleepiness is a universal phenomenon experienced as a symptom in a variety of disorders but also as a typical physiological state occurring in most individuals over a 24-hour period (Shen, Barbera, & Shapiro, 2006). One generally accepted definition of sleepiness is one's tendency or propensity to fall asleep, also known as sleep propensity (Buysse et al., 2006). Fatigue is also commonly reported as a symptom of various disorders, often described as the most severe symptom (Aaronson et al., 1999; Shapiro, 1998, 2004). Fatigue is a subjective feeling of physical and/or mental weariness or tiredness but is not necessarily associated with increased sleep propensity (Buysse et al., 2006). Thus, although these terms have overlapping features, one distinguishing feature is one's ability to fall asleep given the opportunity. Whereas an individual who is sleepy would be able to initiate sleep onset, this would likely not be the case for those with fatigue. Two commonly used validated and recommended scales for the assessment of fatigue (see Buysse et al., 2006) include the Fatigue Severity Scale (FSS) (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989) and the Multidimensional Fatigue Inventory (MFI) (Smets, Garssen, Bonke, & De Haes, 1995). The FSS is a nine-item self-report severity scale that primarily measures the impact of fatigue on specific types of functioning. Likewise, the MFI is a 20-item self-report measure that includes ratings of severity of fatigue over the past week. This measure includes five dimensions, such as general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity. In addition to these two commonly used measures, there are numerous other self-report measures of fatigue.

Despite the significance and prevalence of insomnia in the context of MDD, studies suggest that practitioners have a poor understanding of the disorder. The presence of a sleep complaint or insomnia is the best predictor of whether a patient will receive a depression diagnosis (Krupinski & Tiller, 2001). In a chart review study, a mere

28% of those diagnosed with MDD actually met DSM-IV criteria for this condition; the remaining patients were incorrectly diagnosed with MDD when they actually had untreated insomnia. When an insomnia diagnosis is made, the presence of a mental disorder tends to preclude consideration of primary insomnia, and the presence of conditioned arousal or poor sleep habits tends to preclude consideration of a "related to a mental disorder" diagnosis (Nowell, Buysse, & Reynolds, 1997). Conditioned arousal and poor sleep habits often play a significant role in MDD-I and need to be targeted; however, this tends to be ignored by treatment providers.

The presence of insomnia complicates treatment choices for those with depression. In treating depression, selective serotonin reuptake inhibitors (SSRIs) are the most widely used first-line antidepressant medications because of their favorable side-effect profiles relative to older medication classes. SSRIs are highly effective for treating depression, but their effects on sleep vary as a function of the sleep measures employed. Studies using objective polysomnographic (PSG) indices suggest that one third of SSRI-treated patients experience an architectural worsening of their sleep (Armitage, 2000)—that is, decreased sleep efficiency, increased awakenings, decreased slow-wave sleep, and some sleep disruption in as long as 30 weeks after discontinuation (Armitage, Yonkers, Cole, & Rush, 1997; Keck, Hudson, Dorsey, & Campbell, 1991; Minot, Luthringer, & Macher, 1993; Trivedi, Rush, & Armitage, 1999). In contrast to objective sleep measures, patients report some modest mean sleep improvements (Asnis, Chakraburtty, & DuBoff, 1999; Fava et al., 2006). Insomnia can also be a side effect of SSRI treatment, both in the early acute phase and occasionally as a late-onset problem (Zajecka, Amsterdam, & Quitkin, 1999). A further complication is that residual insomnia can remain in many MDD-I patients even if they otherwise respond to antidepressant therapy (Carney et al., 2007; Nierenberg et al., 1999). Single-drug strategies, most notably with the tricyclic antidepressants amitriptyline and trimipramine, have positive effects on both sleep and mood (Ware, Brown, Moorad, Pittard, & Cobert, 1989), but because of their side effect profile and potential for use in a lethal overdose, they are often an unattractive choice for such patients. Given these observations as well as the deleterious effects persistent insomnia may have on the long-term course of MDD, the use of some antidepressant medications in isolation may be insufficient for the treatment of some MDD-I patients (Walsh & Schweitzer, 1998).

Therapies that target both the mood and sleep difficulties of these patients would seem better suited to their overall treatment needs. One effective strategy for treating SSRI-induced sleep worsening is to add trazodone. Pairing trazodone with an SSRI appears to improve both objective and subjective indices of insomnia; unfortunately this does not appear to enhance depression outcomes (Kaynak, Kaynak, Gozukirmizi, & Guilleminault, 2004). Some randomized controlled trials have tested the merits of recommended sleep-targeted therapies in combination with depression therapies with promising results (Mendelson et al., 2004). One study showed that MDD-I patients achieved greater sleep improvements over a four-week treatment phase in response to SSRI therapy plus zolpidem than when treated via SSRIs alone (Asnis et al., 1999). In a second trial, patients treated with both a SSRI (fluoxetine) and a hypnotic (eszopiclone) showed greater sleep improvements over eight weeks of therapy than did those given only the SSRI only (Fava et al., 2006). Moreover, those receiving combined depression and insomnia therapies showed greater pre-to-posttherapy depression improvements as well. However, both studies considered relatively short treatment periods so it remains unknown whether the benefits of these combined pharmacologic approaches persist over time. Furthermore, the former study showed a worsening of sleep subsequent to hypnotic medication withdrawal so the long-term sleep benefits of such treatments after their discontinuation remains in question.

Given these considerations, CBT-I appears to be a particularly viable treatment for MDD-I since there is no risk of polypharmacy, it is as effective as hypnotic medication, and it produces superior, durable long-term improvements (Edinger, Fins, & Sullivan, 1996; Edinger, Hoelscher, & Marsh, 1992; Edinger & Sampson, 2003; Edinger, Wohlgemuth, Radtke, & Marsh, 2004; Espie, Inglis, Harvey, & Tessier, 2000; Morin, Colecchi, Stone, Sood, & Brink, 1999; Morin, Culbert, & Schwartz, 1994; Morin, Kowatch, Barry, & Walton, 1993; Morin, Kowatch, & Wade, 1989; Perlis, Aloia, & Millikan, 2000). CBT-I employs specific empirically validated approaches designed to eliminate conditioned bedtime arousal, increase sleep drive, and correct circadian abnormalities. The main components of CBT-I include stimulus control, sleep restriction, sleep hygiene, and cognitive therapy. The main objective of stimulus control (Bootzin & Epstein,

2000) is to break this conditioned arousal that arises after repeated unsuccessful sleep attempts (Perlis et al., 1997). Weakening of this conditioned arousal is achieved by focusing on reassociating the bed and bedroom with successful sleep attempts. Sleep restriction, another main behavioral component of CBT-I, is a method designed to shorten the amount of time in bed to match the client's total sleep time (Morin et al., 2006). This is determined by evaluating the clients' two-week sleep diary and calculating the total sleep time and adding an additional 30 minutes to allow time to fall asleep. Together with the client, the therapist would determine an earliest rise time that would be consistent each day and work backward to calculate an earliest bedtime. Finally, throughout the course of CBT-I, clients are educated on healthy sleep behaviors and sleep-promoting environmental conditions. These include the elimination or reduction of caffeine, alcohol, and nicotine; engaging in exercise; eating a light bedtime snack with tryptophan; and creating a sleeping environment that is quiet, dark, and comfortable.

CBT-I also targets the belief that one must engage in compensatory sleep behaviors (i.e., behaviors linked to poor sleep) (Edinger et al., 1996; Edinger et al., 1992; Edinger & Sampson, 2003; Edinger et al., 2004; Edinger, Wohlgemuth, Radtke, Marsh, & Quillian, 2001). Cognitive techniques used in CBT-I involve teaching the client to identify, realistically evaluate, and modify sleep related thoughts (Harvey, 2002) (e.g., "if I do not get eight hours of sleep, I will not be able to get through the day tomorrow," or "I need to nap to catch up on lost sleep"). Many of these misconceptions can lead to hyperarousal (i.e., anxiety about not being able to fall asleep and the consequences) and maladaptive compensatory coping strategies (e.g., daytime napping, increased time in bed).

Thus far, research has suggested that CBT-I is highly safe and effective with various insomnia patients. Specifically, these include those with primary insomnia (Edinger et al., 1996; Edinger et al., 1992; Edinger & Sampson, 2003; Edinger et al., 2004; Edinger et al., 2001; Espie et al., 2000; Morin et al., 1999; Morin, Stone, McDonald, & Jones, 1994), MDD (Edinger et al., 2009; Ware et al., 1989; Manber, 2008; Morawetz, 2001; Vallieres, 2000), periodic limb movement disorder (Edinger et al., 1996), mixed psychiatric or medical disorders (Morin, Stone, et al., 1994; Pallesen, Nordhus, & Kvale, 2003; Quesnel, Savard, & Simard, 2003) and pain-related syndromes (Currie, Wilson, Pontefract, & deLaplante, 2000; Morin et al., 1989). CBT-I also appears to affect the neurophysiology implicated in insomnia, as it results in decreased high-frequency activity and increased slow-wave activity in the electroencephalogram (Cervena et al., 2004). Moreover, contrary to the above-noted findings with hypnotic treatment, the gains achieved during CBT-I appear to endure long after the end of active therapy (Edinger et al., 1996; Edinger et al., 1992; Edinger & Sampson, 2003; Edinger et al., 2004; Edinger et al., 2001; Espie et al., 2000; Morin et al., 1999; Morin, Stone, et al., 1994).

Those with MDD-I manifest the type of treatment targets for which CBT-I has been designed (Kohn & Espie, 2005). Those with depression and insomnia exhibit unhelpful beliefs about sleep and display more sleep-disruptive behaviors and greater sleep effort behaviors than those with insomnia alone (Carney et al., 2010; Carney et al., 2007; Kohn & Espie, 2005). Indeed, there are some promising early findings of CBT-I in MDD-I patients. Morawetz (2001) found that the vast majority of MDD-I patients ($N = 86$) treated with a self-help form of CBT-I reported marked depression improvement, in addition to the sleep improvement by treating sleep alone (Morawetz, 2001). Morin and colleagues (2000) showed CBT-I resulted in an improvement for sleep and an associated mood improvement among a series of cases with comorbid insomnia and MDD. Included in these beliefs are that a poor night's sleep will interfere with their activities the following day (Carney, Edinger, et al., 2010). In an effort to compensate for apparent sleep loss, those with insomnia tend to engage in sedentary behaviors (i.e., spending an excessive amount of time in bed, daytime naps, etc.). In fact, relative to good sleepers, poor sleepers have been found to engage in a lower frequency of activities even after accounting for depression. Unfortunately decreasing the frequency of activity may actually lead to poorer sleep, as exercise has been linked to beneficial sleep effects (Kubitz, Landers, Petruzzello, & Han, 1996; O'Connor & Youngstedt, 1995; Youngstedt, O'Connor, & Dishman, 1997) and has been suggested as a potential therapeutic modality in the treatment of sleep disorders (Sherrill, Kotchou, & Quan, 1998). Behavioural activation is commonly used as part of a CBT treatment of MDD (Dimidjian, Barrera, Martell, Munoz, & Lewinsohn, 2011; Martell et al., 2010) and is increasingly being incorporated into treatments of insomnia as well. Increasing activities is beneficial

for the sleep drive, such that people are less sedentary. Moreover, regular activity may act as zeitgebers and help to entrain the circadian clock, thus, also improving the sleep system. Given that both MDD and insomnia are characterized by a reduction in daytime activities, increasing activities, with both mastery and pleasure, have potential benefits for both mood and sleep.

Finally, several studies have documented the efficacy of CBT-I in patients with complex, multiple comorbidities including MDD and PTSD (Edinger et al., 2009). A randomized clinical trial combining SSRI medication with CBT-I showed that in comparison with a SSRI alone, there were greater insomnia symptom and depression symptom improvements (Manber et al., 2008). In fact, the addition of CBT-I to an antidepressant medication resulted in greater rates of depression remission than antidepressant medication alone (Manber et al., 2008). Thus there is growing support for superior depression symptom outcomes by combining depression treatments with sleep treatments, both pharmacologic and CBT-I, over treatments focused on depression only. This approach would be enhanced in the context of providing care in a multidisciplinary team-treatment setting with post-treatment follow-up care.

Other Comorbid Sleep Disorders

Obstructive Sleep Apnea

Aside from chronic insomnia, other sleep disorders that are relevant to depression include apnea, restless legs syndrome, periodic leg movement disorder, and hypersomnia. Obstructive sleep apnea (OSA), the most common form of sleep disordered breathing, is characterized by repetitive episodes of upper airway obstruction during sleep, including sleep-related pauses (apneas) in respiration. Breathing-related sleep disorders are disabling and can have negative consequences on the daily functioning of those affected. Daytime impairments often include excessive daytime sleepiness and sometimes cognitive impairments (Borak, Cieslicki, Koziej, Matuszewski, & Zielinski, 1996; Cheshire, Engleman, Deary, Shapiro, & Douglas, 1992).

Although studies specifically designed to determine the prevalence of comorbid depression and OSA are limited, there appears to be a higher prevalence of depression among this population (Harris, Glozier, Ratnavadivel, & Grunstein, 2009). A large-population telephone survey demonstrated that among those identified with having OSA or another type of breathing-related disorder, the prevalence of MDD was 17%, in comparison with 4.3% of the entire sample (Ohayon, 2003). Another prevalence study examining diagnoses recorded over a four-year period found that among those with clinician-diagnosed OSA, 21.8% also had clinician-diagnosed depression, a significant difference to the 9% of depression in the rest of the sample without apnea (Sharafkhaneh, Giray, Richardson, Young, & Hirshkowitz, 2005). Thus the prevalence of depression among those with OSA in these studies is generally consistent with 3% to 5% in community settings and 5% to 10% in primary care in the United States (Katon, 2003). Those diagnosed with OSA at a sleep clinic generally exhibit higher rates of depression or depressive symptoms.

Possible mechanisms underlying the association between depression and OSA include sleep fragmentation (Schroder & O'Hara, 2005; Sforza, de Saint Hilaire, Pelissolo, Rochat, & Ibanez, 2002; Yue et al., 2003) and hypoxemia (Kamba et al., 2001; Kamba, Suto, Ohta, Inoue, & Matsuda, 1997; McGown et al., 2003). Aside from these two mechanisms, OSA and depression have been suggested to share a common neurobiological risk factor. The serotoninergic system plays an essential role as a neurobiological substrate underlying deficits in the regulations of mood, sleep-wakefulness cycle, and the control of upper airway muscle tone during sleep. Depression is related to a functional decrease of serotoninergic neurotransmission, which largely contributes to the changes in sleep as outlined above (Adrien, 2002), although the exact role of serotonin in the physiology of sleep needs further exploration (Schroder & O'Hara, 2005). Finally, OSA and depression share common risk factors (e.g., obesity, cardiovascular disease, diabetes, etc.), which may partially explain their high rates of comorbidity (Schroder & O'Hara, 2005).

The treatment literature on the effects of successful continuous positive airway pressure (CPAP) therapy for OSA on depression has yielded mixed results. Improvements in depression scores have been reported in some (Kawahara, Akashiba, Akahoshi, & Horie, 2005; Means et al., 2003; Sanchez, Buela-Casal, Bermudez, & Casas-Maldonado, 2001) but not all studies with placebo arms (Munoz, Mayoralas, Barbe, Pericas, & Agusti, 2000). A meta-analysis of randomized controlled trials (RCTs) confirmed that CPAP was effective at reducing sleepiness and improving overall quality of life for those with OSA (Giles et al., 2006). More recent RCTs (Bardwell et al., 2007;

Haensel et al., 2007) failed to find improvements in mood in relation to CPAP, however, both measured outcomes after only two weeks of CPAP treatment. These mixed findings may be a consequence of dissimilar study designs and/or populations, or of measurement issues (Harris et al., 2009). Given the complex relationship between OSA and depression, future research into the assessment and treatment of these comorbid disorders is required. For the time being, clinicians should be cognizant of this association and consider that OSA may be contributing to depressive symptoms in treatment resistant patients. Appropriate referrals to a sleep clinic for evaluation should be initiated in the presence of complaints or evidence of sleepiness, as well as concomitant loud snoring, observed apneas, high blood pressure, and/or nocturia.

Restless Legs Syndrome

Restless legs syndrome (RLS) is a disorder characterized by (1) a compelling urge to move the legs, (2) usually accompanied by unpleasant sensations in the legs, (3) initiation or worsening of symptoms during periods or rest or inactivity, (4) partial or total relief of symptoms when moving the limbs, and a (5) a worsening of the symptoms in the evening or during the night (Allen et al., 2003). RLS symptoms do not result in life-threatening consequences but typically persist chronically and impair the patient's quality of life (Allen et al., 2005; Happe et al., 2009). Moreover, RLS appears to be linked to lifestyle behaviors, adverse effects on daytime functioning (Phillips, Hening, Britz, & Mannino, 2006), and a high occurrence of psychosocial impairment (Abetz et al., 2004; Allen et al., 2005; Berger, Luedemann, Trenkwalder, John, & Kessler, 2004).

Patients with RLS often complain of fatigue, disturbed sleep, diminished concentration, psychomotor agitation, and all symptoms that could either be interpreted as symptoms of depression or as a consequence of a sleep disorder (Allen et al., 2003; Earley, 2003). Correlational studies have found a link between the severity of RLS and depression symptoms (Cuellar et al., 2007; Rothdach, Trenkwalder, Haberstock, Keil, & Berger, 2000; Sevim et al., 2004; Winkelman, Finn, & Young, 2006); in a meta-analysis (Picchietti & Winkelman, 2005), depression symptoms were more common among those with RLS than those without RLS. A potential underlying mechanism of RLS and depression may include the dysregulation of CNS dopaminergic metabolism (Hornyak, 2010). Owing to the association between insomnia and depression, sustained sleep disturbances in RLS may further contribute to increased rates of depression in this population.

Given the symptom overlap between RLS and depression, making a diagnosis of either disorder could be challenging. It is suggested that symptoms typical of depression be assigned to depression, even in the case of symptom overlap (Hornyak, 2010). Clinicians should be mindful of that fact that depression treatment may be unsuccessful if the patient continues to experience sleep difficulties due to the RLS (Hornyak, 2010; Hornyak et al., 2009). Given the unclear relationship between RLS and antidepressant medications, one consideration is to combine RLS treatment with an empirically supported psychotherapy for depression (Chambless & Hollon, 1998), such as interpersonal psychotherapy (IPT) or cognitive behavior therapy for depression (CBT-D). Thus the assessment and treatment of RLS is an essential component of a sound treatment plan and could have beneficial effects for the mood disorder.

Periodic Limb Movement Disorder

Periodic limb movements in sleep (PLMs) are characterized by brief (0.5- to 5.0-second) movements of the lower extremity during sleep; these tend to occur at 20- to 40-second intervals, most often in the first three hours of sleep (American Academy of Sleep Medicine, 2005; Atlas Task Force, 1993). Periodic limb movement disorder (PLMD) is diagnosed when PLMs exceed norms for the patient's age, are resulting in sleep disturbance, and occur in the absence of another primary sleep disorder or reason for the PLMs (American Academy of Sleep Medicine, 2005). It is common for an individual with PLMs to be unaware of the movements or of the transient arousals. The majority of individuals with RLS have PLMs (Silber et al., 2004), although PLMs are not specific to RLS. Studies have shown elevated rates of depression among those with PLMD compared to controls (Aikens, Vanable, Tadimeti, Caruana-Montaldo, & Mendelson, 1999; Mendelson, 1996; Saletu et al., 2002). Treatments for PLMD are generally pharmacologic in nature. However, since some antidepressant medications can increase PLMs (Dorsey, Lukas, & Cunningham, 1996), one consideration is to combine a dopaminergic agent with an empirically supported nonpharmacologic depression treatment (e.g., IPT or CBT-D; Chambless & Hollon, 1998).

Hypersomnia

Hypersomnia is defined by a combination of prolonged nocturnal sleep episodes, increased

nighttime wakefulness, excessive daytime sleepiness, and frequent napping. However, the duration of nightly hypersomniac sleep episodes or the severity of daytime fatigue has not been quantified, leaving this up to the clinician's judgment (Kaplan & Harvey, 2009). Hypersomnia is listed as a symptom for several mood disorders in the DSM-IV-TR (American Psychiatric Association, 2000), including major depressive disorder, bipolar disorder, seasonal affective disorder, and dysthymia.

Prevalence rates of hypersomnia across the mood disorders greatly differ across ages and studies, ranging from 8.9% in children (Williamson et al., 2000) to 75.8% in young adults (Parker et al., 2006). These rates also differ across sex, such that hypersomnia appears to be more common in females than males with MDD (Parker et al., 2006). Khan and colleagues (2002) surveyed 201 opposite-sex twin pairs and found that females reported significantly more hypersomnia while depressed, while the males reported increased rates of insomnia complaints in a depressive episode. Hypersomnia is also prevalent across other mood disorders; however, this is beyond the scope of this chapter.

Although the underlying biological mechanisms between MDD and hypersomnia remain ambiguous, this relationship between hypersomnia and atypical depression is more clearly understood. It has been suggested that a reduced sensitivity to corticotropin-releasing hormone may be involved in the hypersomnia, hyperphagia, and leaden paralysis associated with atypical depression (Gold, Licinio, Wong, & Chrousos, 1995). Moreover, hyperarousal from the hypothalamic-pituitary-adrenal axis and associated corticotropin-releasing hormone deficiency may be responsible for the reverse vegetative symptoms of atypical depression. In regard to psychological mechanisms, it has been suggested that hypersomnia may serve as an avoidance coping strategy (Jacobson, Martell, & Dimidjian, 2001). Kaplan and Harvey (2009) posit that hypersomnia may contribute to the development and/or maintenance of mood disorders and that it in itself is a mechanism. For example, depression-like symptoms often occur after single episodes of extended sleep (Globus, 1969) and extended sleep is predictive of future psychiatric disorders (Breslau et al., 1996; Ford & Kamerow, 1989). Moreover hypersomnia persists even after other symptoms in MDD have remitted (Worthington et al., 1995); further research is warranted into the exact role of hypersomnia in mood disorders.

Given the discrepancy surrounding the classification of hypersomnia, challenges in assessing for this disorder exist. Whereas the DSM-IV-TR and ICD-10 (WHO, 1993) recommend self-reported sleep, the ICSD-II suggests polysomnographic (PSG) monitoring to evaluate sleep efficiency and increased nighttime wakefulness. Various self-report, semistructured clinical interviews, and objective polysomnographic techniques are available for identifying and assessing hypersomnia (Kaplan & Harvey, 2009). The Epworth Sleepiness Scale (ESS) (Johns, 1991) and The Stanford Sleepiness Scale (SSS) (Herscovitch & Broughton, 1981) are two validated and useful tools that provide information on daytime sleepiness and sleep propensity. In addition, The Duke Structured Interview for Sleep Disorders (DSISD) (Edinger et al., 2004) is designed to determine whether an individual has self-reported hypersomnia or any of the other aforementioned sleep disorders that could account for the hypersomnia. In treating those with hypersomnia associated with MDD, medications associated with increased sleepiness are typically not recommended (Baldwin & Papakostas, 2006).

Clinical Guidelines for Practitioners

Of the most important tasks for the treatment provider treating depression in the context of a sleep problem is to conduct a proper assessment for comorbid sleep disorders. Undetected sleep disorders such as sleep apnea are associated with depression (Millman, Fogel, McNamara, & Carlisle, 1989; Pochat, Ferber, & Lemoine, 1993), and successful treatment of apnea can be associated with mood improvements (Sanchez et al., 2001). Moreover, failure to detect sleep apnea would limit treatment response and the breathing disturbance could worsen with the addition of sleep medications (Kryger, 1992). Similarly, periodic limb movement disorder is associated with depression, and a failure to detect and treat this disorder could prevent optimal depression response. Also complicating clinical decision making is the fact that some antidepressant medications worsen leg movements (Damsa et al., 2004; Stahl & Grady, 2003); the detection and treatment of occult sleep disorders are an important parts of effective depression management.

Some antidepressant medications may produce sleep benefits for some, but practitioners should keep in mind that response may vary widely. Whereas combining sleep and antidepressant medications produce greater depression treatment response as well as greater sleep improvement than

antidepressants alone (Fava et al., 2006), most people with MDD have chronic insomnia; therefore the frontline recommended treatment for chronic insomnia is CBT-I (National Institute of Health State of the Science Conference Statement, 2005). Pairing a brief, durable treatment such as CBT-I with an effective depression treatment may be maximally beneficial. Rate of relapse to depression are quite substantial, with over half of those who have experience one depressive episode likely to have another, and the majority of individuals with three episodes being at risk for a fourth episode (Richards & Perri, 2010). The rate of depression remission for those on an antidepressant alone (33%) (Manber et al., 2008) matched the rate (33%) reported for an antidepressant-alone arm in a similar combined sleep and depression treatment trial (Fava et al., 2006); these rates are also similar (37%) to the rate reported in level 1 of the STAR*D study (Warden, Rush, Trivedi, Fava, & Wisniewski, 2007). What differed between the Fava et al. (2006) and Manber et al. (2008) studies above were the rates of depression remission between the treatment arms that combined sleep treatment with the antidepressant. That is, in the Fava et al. (2006) study, depression remission rates were significantly improved to 42% when a hypnotic medication was added to the antidepressant; the rate of depression remission when CBT-I was added to an antidepressant (instead of a hypnotic medication) improved to 67% (Manber et al. 2008). This study requires replication; however, it suggests that combining depression treatment strategies with effective sleep strategies, most notably CBT-I, produces markedly superior depression outcomes to antidepressants alone. It should be explicitly stated that supervision of pharmacologic components of treatment should be provided by only those practitioners who are licensed, expert, and readily available for consults with their patients and with the multidisciplinary team of practitioners who are involved in these cases.

Conclusions

In sum, those MDD patients with significant sleep problems represent a large, vulnerable, and challenging group to treat. Recognizing clinically significant sleep problems, especially those that may account for the depression, and treating the sleep problems of those with depression—including OSA, RLS, PLMD, hypersomnia and insomnia—is of the utmost importance. Insomnia is of the most common sleep problems encountered by MDD patients. Treating the depression only and hoping the insomnia will resolve (whether the insomnia was caused by the antidepressant or premorbid) is a dated practice and not empirically supported. Adding an effective sleep medication or CBT-I has been linked to a resolution of the residual insomnia problem and greater rates of depressive remission. Moreover, most effective treatments for MDD (e.g., IPT or CBT) can easily be combined with CBT-I for those with comorbid conditions and would likely have therapeutic benefits.

Future Directions

There are many questions to be answered in order to improve the lives of those with depression and sleep problems.

1. Arguably the number one problem to solve in this area is to test what combinations and sequencing of sleep and depression treatments are optimal.

2. Several studies have suggested that brief CBT-I can be taught and implemented in general practice settings by providers who are not specialists in mental health or sleep disorders (e.g., Edinger & Sampson, 2004; Espie et al., 2007; Germain et al., 2006). Given the promise of CBT-I for improving both insomnia and MDD outcomes, we will need to find ways to make this treatment more readily available; that is, further strategies to disseminate and test treatments in the settings wherein such patients present (e.g., primary care, general mental health clinics).

3. Our hope is to find/test a single agent (i.e., one medication) with (1) a low side-effect profile, (2) low abuse potential, (3) low potential for lethality in overdose, and (4) effective amelioration of the full complement of sleep and mood problems, including fatigue.

4. We also seek to develop or refine existing assessment tools that discriminate between the overlapping symptoms of MDD and hypersomnia/insomnia. It is not meaningful to remove sleep items from a depression measure to address overlap because there are many more nondiscriminating items that remain (e.g., fatigue) (Beck, Steer, & Brown, 1996; Carney et al., 2012).

5. We must also investigate the utility of revisions in the diagnostic criteria for these disorders so as to reduce or eliminate the overlap between highly comorbid conditions such as chronic insomnia and MDD.

6. It will be helpful to have further investigations of sleep treatments as a preventive

strategy, for reducing depression and comorbid sleep disorders.

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CHAPTER

23 Multiple Sclerosis

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Abstract

Multiple sclerosis (MS) is a chronic disease that affects the central nervous system and can cause a wide variety of both physical and cognitive deficits. Mood disturbances are common, with as many as 50% of patients receiving a diagnosis of major depression during their lifetime. The risk of suicide is high and leaving depression untreated is associated with a host of additional MS symptoms. Depression in MS presents clinicians with unique challenges, as it is often difficult to distinguish from common neurological symptoms. The authors discuss recommended screening tools and therapeutic methods that can assist the clinician in successfully identifying and treating depression in MS.

Key Words: depression, multiple sclerosis, cognitive-behavioral therapy, pharmacotherapy, assessment

Introduction

What Is Multiple Sclerosis?

Multiple sclerosis (MS) is a chronic, inflammatory, autoimmune disease characterized by demyelination of axons in the central nervous system (Compston & Coles, 2008; Pryse-Phillips & Costello, 2001). This demyelination disrupts communications between nerve pathways, frequently causing inefficiencies and/or interruptions in functional systems. As a result, people with MS can exhibit varied expressions of sensory, motor, cognitive, and emotional difficulties (Compston & Coles, 2008). The cause of MS is unclear (Compston & Coles, 2008). A variety of environmental risk factors are currently under investigation, including vitamin D deficiency, cigarette smoking, and infection with viruses such as Epstein-Barr and measles (Ascherio & Munger, 2007a, 2007b; Fernandes de Abreu, Eyles, & Féron, 2009; Wingerchuk, 2011). Similarly, researchers are working to better understand genetic risk factors associated with the development of MS (e.g., see The International Multiple Sclerosis Genetics Consortium, 2011). Diagnostic concordance rates between female monozygotic twins is approximately 33%; in contrast, concordance rates for dizygotic twins is approximately 2%–5% (Ebers, 2008). The strongest genetic risks have been identified within the human leukocyte antigen gene cluster, though genome-wide association studies have also identified many additional genetic loci associated with MS (Berlinga-Taylor et al., 2011; The International Multiple Sclerosis Genetics Consortium et al., 2011).

Prevalence and Common Symptoms

Although MS is most frequently diagnosed among young adult Caucasian women (Cree et al., 2004; Wallin, Page, & Kurtzke, 2004), individuals of other ethnic groups and men are also affected by the disease. Prevalence of MS across the globe varies depending on racial and ethnic heritage, geographic location, and one's proximity to the equator during the first 15 years of life (Compston & Coles, 2008; Rosati, 2001). People born in temperate regions of the globe are more likely to develop the disease than are people born in tropical regions. Approximately

150 individuals per 100,000 are diagnosed with MS in temperate regions (Rosati, 2001). The inflammation and demyelination that occur in the CNS produce lesions that are visible using magnetic resonance imaging (MRI) (see Figure 23.1; Compston & Coles, 2008). Diagnostic criteria require an individual to show lesion activity in the CNS that is disseminated in both space and time, meaning that there must be evidence of lesions in separate locations and instances (Polman et al., 2011). MS patients can experience a wide range of symptoms, depending on the location of lesions or extent of damage. Common symptoms include depression and anxiety, fatigue, pain, tactile and physical disabilities, vision disturbances, coordination and balance problems, spasticity, bowel and bladder incontinence, sexual dysfunction, and cognitive difficulties (Arnett, Barwick, & Beeney, 2008; Benedict et al., 2005; Bruce & Arnett, 2009; Bruce, Bruce & Arnett, 2007; Bruce, Polen, & Arnett, 2007; Pinkston, Kablinger, & Alekseeva, 2007).

Subtypes

There are four subtypes of MS: relapsing-remitting, secondary-progressive, progressive-relapsing, and primary progressive (see Figure 23.2; Lublin & Reingold, 1996). Approximately 75% of patients present with the relapsing-remitting subtype, which is characterized by frequent relapses during which new or worsened symptoms occur (called exacerbations). These periods are followed by remission, during which time the patient either fully or partially recovers from acute symptoms (Pryse-Phillips & Costello, 2001). Within 10 years of diagnosis, approximately 50%–65% of relapsing-remitting patients will shift to a secondary-progressive course (Compston & Coles, 2008). Secondary-progressive MS is characterized by a steady progression of CNS damage that may or may not include occasional exacerbations. Over time, remaining exacerbations dissipate, and a steady progression of the disease ensues leading to increased overall disability (Pryse-Philips & Costello, 2001). Approximately 20% of patients

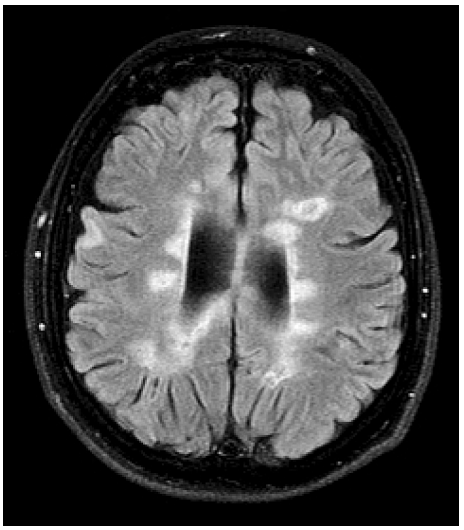

Figure 23.1 A T-1 weighted Magnetic Resonance Imaging scan of a brain with lesions indicative of relapsing-remitting multiple sclerosis. Bright spots on the scan indicate lesions, or areas affected by inflammation and demyelination.

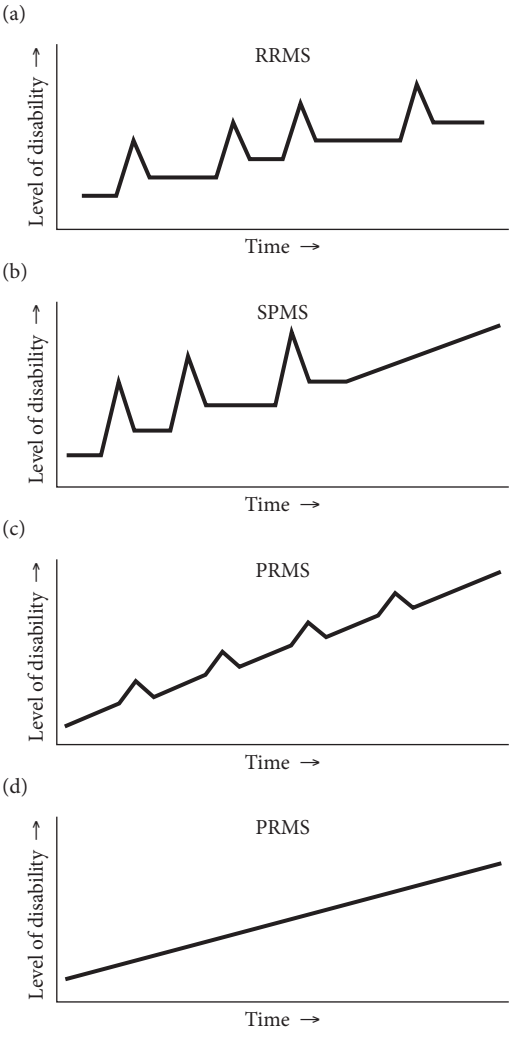

Figure 23.2 Visual depiction of the disease course in the four subtypes of multiple sclerosis. Spikes in disability represent exacerbations.

RRMS = relapsing-remitting multiple sclerosis,
SPMS = secondary-progressive multiple sclerosis,
PRMS = progressive-relapsing multiple sclerosis, and
PPMS = primary-progressive multiple sclerosis.

initially present with primary-progressive MS (Compston & Coles, 2008). This course is characterized by gradual progression of disease and disability without exacerbations or relative periods of remission. Finally, approximately 5% of patients present with a progressive-relapsing course characterized by a progression of the disease and disability with both exacerbations and periods of remission.

Treatment

There is no cure for MS. Patient care typically involves the use of disease-modifying therapies (DMTs), steroids to manage acute relapses, and treatments that target specific symptoms unique to the individual (Kieseier, Wiendl, Leussink, & Stüve, 2008). DMTs are medications that are specifically designed to slow disease progression and reduce the frequency of exacerbations in relapsing-remitting disease (Goodin, 2008; Jacobs et al., 1996; Johnson et al., 1995; Kieseier et al., 2008; The IFNB Multiple Sclerosis Study Group, 1993). There are several DMT approved by the Food and Drug Administration for treating MS, including interferon β-1a, interferon β-1b, glatiramer acetate, mitoxantrone, natalizumab, and fingolimod (Kieseier et al., 2008; Pozzilli, Prosperini, & Borriello, 2011). Clinical trials have shown that DMT reduce the incidence of exacerbations (between 28% and 78%), new lesion formation (between 36% and 83%), and progression of overall disability (between 30% and 75%), compared with placebo (Berger, 2011; Duddy et al., 2011; Kieseier & Stüve, 2011). With the exception of 3 newly FDA approved oral medications, DMTs are administered via intravenous infusion or intramuscular or subcutaneous injection. Although these medications are most commonly prescribed to individuals with relapsing-remitting MS, interferon β-1b and mitoxantrone have been approved for use among patients with a progressive disease course (Duddy et al., 2011). Despite Food and Drug Administration approval, some researchers have suggested that the efficacy of these agents in progressive disease is not well established (Ehling, Berger, & Reindl, 2010).

Though DMT are considered standard treatment to prevent ongoing progression of the disease, these drugs present patients with troublesome physical and psychological barriers that can affect adherence (Walther & Hohlfeld, 1999; Verdun di Cantogno, Russell, & Snow, 2011; Zivadinov et al., 2003). As many as 75% of patients experience unwanted side effects from these medications, including painful injection site reactions, flu-like symptoms, depression, fatigue, and increased spasticity (Derwenskus, 2011). Additionally, approximately 50% of patients have reported difficulty with injections and needle phobia (Mohr, Boudewyn, Likosky, Levine, & Goodkin, 2001; Verdun di Cantogno et al., 2011). Approximately half of MS patients do not properly adhere to their prescribed DMTs (Bruce, Hancock, & Lynch, 2010; Fraser, Hadjimichael, & Vollmer, 2003; Wong, Gomes, Mamdani, Manno, & O'Connor, 2011), which can result in new CNS lesion development, an increase in exacerbations, and poorer overall quality of life (Bruce, Hancock, Arnett, & Lynch, 2010; Clerico, Barbero, Contessa, Ferrero, & Durelli, 2007; Coyle, 2008, 2009). Research has linked poor DMT adherence to psychiatric and personality factors, in addition to cognitive problems (Bruce et al., 2010; Mohr et al., 1997). Unfortunately, MS patients' adherence problems may be ingrained. The medications that are so important in preventing further decline often have negative immediate side effects, and any positive benefit of taking the medication is long term and not clearly observable to the patient.

Finally, treatment of MS also involves the use of symptom-specific therapies (Compston & Coles, 2008). These treatments may involve medications to address muscle stiffness and spasms, urinary and bowel incontinence, sexual dysfunction, pain, fatigue, and psychiatric comorbidities (Samkoff & Goodwin, 2011). Additionally, physical and speech therapists use therapies and assistive devices to address symptoms such as pain, balance problems, or difficulty swallowing (Compston & Coles, 2008). Successful treatment of MS and MS-related symptoms often includes both DMTs and treatments that target specific symptoms experienced by the patient.

Depression in MS

Comorbid depression presents clinicians with unique challenges: it occurs very frequently, it is often difficult to distinguish from symptoms of MS, and it is associated with several other signs of neurological disease. Despite these challenges, a significant body of research exists that can guide the successful assessment and treatment of comorbid depression in MS. Though the etiology of depression in MS is likely multifactorial, clinical practice and research consistently indicate that depression in MS responds well to treatment and patients benefit greatly from prompt clinician attention. In fact, it is essential that clinicians treat depression in MS, as

research suggests that patients who do not receive treatment for depression will most likely remain depressed, and may be at risk for a worsening depression over time (Mohr et al., 1999).

Depression is the most common psychiatric comorbidity in MS, with as many as 50% of MS patients experiencing major depression during the course of their disease (Alajbegovic et al., 2011; Sadovnick et al., 1996; Siegert & Abernethy, 2005). Lifetime prevalence rates of depression are significantly higher among MS patients than among individuals in the general population (10%–15%) and in other chronic disease groups (American Psychiatric Association, 2000; Patten, Beck, Williams, Barbui, & Metz, 2003). Point prevalence rates of depression in MS range from 14% to 25.7% (Patten et al., 2003; Schiffer, 2009). Other estimates suggest that approximately one in six MS patients has undiagnosed or untreated depression (Marrie et al., 2009). Depression in MS patients is associated with several real-world difficulties, including significant impairments in social and work functioning (Goldman Consensus Group, 2005). Depression also contributes to an increased rate of suicide in MS patients. Given the myriad negative consequences, the accurate assessment and treatment of depression in MS are of utmost importance.

Suicide Risk in MS

As many as 15% of deaths in MS can be attributed to suicide, a rate that ranges from approximately 2.3 to 7.5 times greater than suicide rates in the general population (Fredrickson, Cheng, Jiang, & Wasserman, 2003; Sadovnick, Eisen, Ebers, & Paty, 1991). Factors that are associated with the incidence of suicide in MS include the high rate of depression (Alajbegovic et al., 2011; Sadovnick et al., 1996; Siegert & Abernethy, 2005), a high rate of untreated depression (Caine & Schwid, 2002), evidence that interferon-β might increase depressive symptoms and suicidality (Fragroso et al., 2010), and difficulty coping with effects of the disease (Feinstein, Kartsounis, Miller, Youl, & Ron, 1992). Currently, there are no tools that have been validated for suicide screening in MS patients. Future studies should examine the clinical utility of tools such as the Beck Scale for Suicide Ideation (Beck, Kovacs, & Weissman, 1979) for use with MS patients. Clinicians should be aware that while MS is not usually terminal, its effects can be debilitating and patients may benefit from additional support and careful assessment of mood symptoms and suicidality.

Assessment of Depression in MS

Assessing the presence of depressive symptoms in MS can be challenging. There is a large degree of overlap between the vegetative symptoms of depression and the neurological symptoms commonly experienced as part of MS (Alajbegovic et al., 2011). Specifically, MS patients frequently experience fatigue, disturbance of sleep, sexual dysfunction, appetite changes, weight loss, psychomotor slowing, and cognitive deficits (Mohr et al., 1997; Patten, Berzins, & Metz, 2010). These neurovegetative symptoms can occur as part of depression or general neurological deterioration in both depressed and nondepressed MS patients. Additionally, some researchers have suggested that inflammatory processes in the brain may be inextricably linked with depressive pathology (Patten, 2010). Because of the high degree of symptom overlap, caution is warranted when interpreting symptoms and evaluating depression in MS patients. Specifically, clinicians must consider whether the severity of particular symptoms surpasses what would be expected given the disease, or whether the symptoms might be related to underlying depression.

Another challenge in assessing for the presence of depression in MS patients is the possibility that patients may suffer from pseudobulbar affect, which is an affective disinhibition syndrome whereby individuals are unable to control their emotions (de Seze et al., 2006). The neural mechanisms underlying this phenomenon are not well understood. One theory posits that damage caused by MS disease processes (e.g., lesions) interrupts the ability of the frontal cortex to appropriately inhibit emotional expression regions in limbic and upper brainstem areas that are involved in appropriately adjusting one's behavior in social contexts (Parvizi, Anderson, Martin, Damasio, & Damasio, 2001). Patients who have pseudobulbar affect experience involuntary crying or laughing outbursts that may be incongruent to their true mood state. Pseudobulbar affect (also called pathological laughing and crying) occurs in approximately 10% of MS patients and can co-occur with depression (de Seze et al., 2006; Smith et al., 2004), potentially confounding the clinician's appraisal of outward mood symptoms. Currently, the recommended treatment for pseudobulbar affect in MS patients involves using a combination of dextromethorphan and quinidine (Garnock-Jones, 2011; Pioro et al., 2010). In addition, neuropsychological counseling that includes education, social skills training, and behavior modification may reduce inappropriate social behaviors (Benedict et al., 2000).

Recently, researchers proposed a framework to assist clinicians in the accurate assessment of MS-related depression (Strober & Arnett, 2010). This diagnostic model uses a "trunk and branch" approach. Trunk symptoms are found in both depressed and nondepressed individuals with MS; branch symptoms are only endorsed by depressed patients with MS. In a study of depressed and nondepressed MS patients and controls, Strober and Arnett (2010) found that branch symptoms such as pessimism, guilt, disappointment, sadness, sense of failure, and changes in appetite or weight were commonly endorsed by depressed MS patients, but not nondepressed MS patients. In contrast, symptoms that were endorsed in similar numbers by both depressed and nondepressed MS patients ("trunk" symptoms) included fatigue, indecision, loss of libido, work difficulty, irritability, loss of interest, crying, dissatisfaction, and self-criticism. They argued that although "branch" symptoms indicate possible depression in MS, some "trunk" symptoms may also indicate depression, especially if they are present in excess of what would be typically expected in the disease.

Two self-report assessment tools have also shown promise as screens for depression in MS: the Chicago Multiscale Depression Inventory (CMDI; Nyenhuis et al., 1995) and the Beck Depression Inventory—Fast Screen (BDI-FS; Beck, Steer, & Brown, 2000). The CMDI is a 50-item self-report measure that was developed on a three-scale structure: mood, evaluative, and vegetative symptoms. Therefore, the CMDI can distinguish vegetative from nonvegetative symptoms of depression to reduce the potential for confounds with neurological symptoms. Chang and colleagues (2003) evaluated the CMDI's subscales in a large group of MS patients and found good internal consistency and confirmed the three-factor structure. It should be noted that MS patients endorsed items assessing fatigue and uselessness differently than the original normative sample, and the authors stated that endorsement of these items may not always be indicative of underlying depression in MS. A cutoff score of 23 (94% sensitivity and 84% specificity) on the mood subscale and of 21(71% sensitivity and 91% specificity) on the evaluative subscale have been recommended for MS patients, as these scores were able to reliably distinguish true cases of clinical depression from subclinical symptomatology (Stober & Arnett, 2009).

The BDI-FS is a brief seven-item self-report measure developed specifically for use with medical patients whose symptoms might confound the accurate assessment of depression. Benedict and colleagues (2001) found that scores on this measure correlated strongly with informant-based data and other self-report measures of depression in MS. A cutoff score of 4 has been recommended for MS patients, as this score was able to distinguish true cases of clinical depression from subclinical symptomatology with 94% sensitivity and 82% specificity (Stober & Arnett, 2009). Although the CMDI and BDI-FS are recommended to assist the clinician in screening for depression in MS, a diagnosis of depression should only be made following a thorough clinical interview.

Treatment of Depression in MS

Depression in MS tends to respond well to psychotherapeutic treatment. Cognitive-behavioral therapy (CBT) has been shown to effectively treat depression among numerous patient groups (APA Task Force on Evidence-Based Practice, 2006). There is strong evidence that it is also efficacious in treating depression in MS patients. For instance, in one study, researchers conducted a randomized controlled trial of telephone-based CBT compared with usual care for MS patients (Mohr et al., 2000). Telephone-based treatment is particularly attractive as an option for MS patients because the disease can cause physical disability that results in mobility and transportation problems. The CBT-based protocol was adapted specifically for working with MS patients. Participants received a workbook titled "Coping with MS" that included visual aids that clinicians could refer to by telephone, help with homework assignments, and serve as a reminder of the key topics covered in sessions. Treatment consisted of goal development, thought monitoring, and identifying and challenging cognitive distortions. When necessary, clinicians also included modules on pleasant event scheduling and fatigue management. Following 8 weeks of treatment, MS patients reported significant reductions in depressive symptomatology, while the usual care group reported no change in symptoms. Ratings on a self-report measure of depression decreased by 44% in the treatment group, compared with a decrease of only 4.4% in the usual care group. These treatment materials have now been published in the *Treatments That Work* series, available from Oxford University Press (Mohr, 2010a, 2010b).

In another study, researchers randomized depressed MS patients into one of three treatment groups: CBT, supportive group therapy, and sertraline

(a selective serotonin reuptake inhibitor; SSRI; Mohr, Boudewyn, Goodkin, Bostrom, & Epstein, 2001). The CBT group participants attended 16 individual therapy sessions that focused on the use of behavioral activation and cognitive restructuring techniques. Additionally, these sessions contained techniques adapted specifically for MS patients, such as management of fatigue, pain, stress, social difficulties, and mild cognitive impairment. The supportive therapy group participants received 16 group therapy sessions that focused on interpersonal group processes and emotional expression of issues related to coping with MS. Participants in the sertraline group were started at a 50-mg/day dosage and incrementally increased to 200 mg/day or until full remission of symptoms was achieved. Results indicated that CBT and sertraline were superior to supportive group therapy in reducing depressive symptoms, as measured by the Beck Depression Inventory (BDI) and Hamilton Rating Scale for Depression (HRSD). Sertraline treatment was as effective as CBT at lowering BDI scores but less effective than CBT at lowering HRSD scores. Following treatment, 40% of the CBT group and 38% of the sertraline group no longer met diagnostic criteria for depression, compared with only 9% of the supportive therapy group.

Group therapy has also shown some promise in treating depression in MS. Lincoln and colleagues (2011) devised an adjustment group treatment format, which consisted of six 2-hour sessions over a 12-week period. Participants were randomly assigned to a treatment group or waitlist control group. The supportive treatment was based on cognitive-behavioral principles and delivered in a small-group format (eight participants per group.) Researchers collected self-report data on depression at baseline and 4 months and 8 months posttreatment. Only individuals with elevated scores on the General Health Questionnaire or the Hospital Anxiety and Depression Scale (HADS) were eligible for inclusion. Results indicated that the treatment successfully decreased scores on both the BDI and HADS and that these changes were still present at the eight-month follow-up. Specifically, scores on the BDI decreased by 29% and scores on the HADS decreased by 20% from baseline for treatment group participants at the 8-month follow up. No significant changes were reported for control group participants.

Mindfulness training has also been examined as a method of treating depression in groups of MS patients. Grossman and colleagues (2010) conducted a randomized controlled trial of mindfulness-based training in a group of relapsing-remitting and secondary-progressive MS patients. Treatment involved an individual intake interview, eight 2½-hour group therapy sessions delivered over 8 weeks (10–15 patients per group), one 7-hour group session, daily homework, and an individual final session. The study also included a control group whose members received medical treatment as usual. Results indicated that the mindfulness-based protocol significantly reduced levels of self-reported depression on the Center for Epidemiological Studies–Depression Scale (CES-D) immediately following the intervention. Following treatment, scores on the CES-D decreased from baseline by 32% for treatment group participants compared with an increase of 9% for control group participants. Six months posttreatment, patients assigned to the treatment group still showed significant, albeit diminished, improvement in depressive symptoms. Additional research into the efficacy of group delivered treatments for depression is encouraged. Groups not only allow providers to maximize productivity, but also offer patients the opportunity to glean support from one another.

As noted, depression in MS has also been successfully treated with pharmacotherapy agents. Schiffer and Wineman (1990) randomly assigned participants into a group receiving desipramine (a tricyclic antidepressant) and individual psychotherapy, or placebo with individual psychotherapy. Results indicated that participants in the group treated with 150 mg of desipramine showed a significant decrease in scores on the HRSD following treatment, but not the BDI. These results suggest that adjunctive pharmacotherapy might be beneficial in addition to psychotherapy to treat depression in MS. Another study randomized participants into a group treated with 40 mg of paroxetine (an SSRI) or placebo (Ehde et al., 2008). Both groups showed improvement following 12 weeks of treatment, with 40% of the placebo group and 57% of the treatment group showing at least a 50% reduction in HRSD scores. In a meta-analysis of key depression treatment studies, Mohr and colleagues (1999) found that both therapy and pharmacotherapy led to a reduction in levels of depression. Similarly, the Goldman Consensus Group on the treatment of depression in MS (2005) recommended treating depression with both CBT and antidepressant medication for the best results.

Secondary Outcomes of Treating Depression in MS

Treatment of depression in MS also has secondary positive effects for patients. Nearly 63% of

patients with at least one comorbid mood or anxiety disorder demonstrate variable/poor adherence to their DMT. In contrast, only 13% of patients with no comorbid depression or anxiety disorder exhibit variable/poor adherence (Bruce et al., 2010). Treating depression may improve adherence to DMTs in MS. In one sample, depressed MS patients taking DMTs were approximately half as likely to be adherent to disease-modifying medication than were patients who were not depressed (Tarrants, Oleen-Burkey, Castelli-Haley, & Lage, 2011). Depressed patients who were on antidepressant therapy for at least 6 months demonstrated better adherence to disease-modifying medication than depressed patients who were not taking antidepressants or those who had been taking them for less than 6 months. Caution must be used when interpreting this relationship, however, as it may be explained by the fact that individuals who are adherent to one medication are more likely to be adherent to another medication. Further research in this area is needed in order to extrapolate the underlying factors contributing to this relationship.

Positive secondary effects were also illustrated in a randomized controlled trial of telephone-based depression treatment. Researchers found that adherence to interferon β-1a was greater for individuals in a CBT group than a usual care group at a 4-month follow-up (Mohr et al., 2000). Another study showed an effect of greater DMT adherence following depression treatment (Mohr et al., 1997). Eighty-six percent of depressed patients who received psychotherapy or antidepressant medication continued their DMT, compared with just 38% of the depressed patients who did not receive treatment for depression. Taken together, this research shows that adherence to disease-modifying medications is associated with depression and that treatment of depression improves adherence to disease-modifying medications. By improving disease-modifying medication adherence, treatment of depression likely reduces relapse rates and slows overall disease progression in MS.

In addition to improving adherence, treatment of depression reduces fatigue, an omnipresent and debilitating symptom of MS (Kinsinger et al., 2010). Furthermore, successfully treating depression may cause beneficial immunological changes in the body (Mohr, Goodkin, Islar, Hauser, & Genain, 2001). Specifically, depression in MS is associated with increased production of interferon-γ, a proinflammatory cytokine that is elevated during exacerbations. The successful treatment of depression in MS patients has been associated with a significant decline in the production of interferon-γ.

Treating depression has also been shown to improve subjective complaints of cognitive deficits. Many patients with MS report cognitive deficits, but these reports are not always indicative of measurable cognitive decline (Bruce & Arnett, 2004; Bruce, Bruce, Hancock, & Lynch, 2010). In fact, researchers have established that many MS patients perceive themselves to have cognitive deficits that are not substantiated with neuropsychological testing (Benedict et al., 2003; Middleton, Denney, Lynch, & Parmenter, 2006). Perceived cognitive deficits can be distressing to patients and are often associated with depression (Maor, Olmer, & Mozes, 2001). Changes in both self-reported depression and fatigue following treatment with CBT and supportive emotion focused therapy were shown to predict changes in subjective reports of cognitive problems, but not objectively measured cognitive skills (Kinsinger, Lattie, & Mohr, 2010). In sum, treating depression in MS has effects that reach beyond improvements in mood.

Factors Associated With Depression in MS

A large body of research focuses on identifying factors associated with depression in MS. The cause of depression in MS is likely varied with contributors such as fatigue, low levels of social support, exacerbations of MS symptoms, brain atrophy, genetic predisposition, and poor overall quality of life. Presented next are some of the most commonly investigated contributors.

FATIGUE

Between 75% and 100% of MS patients report experiencing excessive fatigue over the course of the disease (Egner, Phillips, Vora, & Wiggers, 2003; Ziemssen, 2009). Fatigue can generally be defined as a lack of energy required to engage in physical or mental activities (Aaronson et al., 1999). Fatigue can have a large impact on quality of life, and patients often describe it as the worst symptom of the disease (Fisk, Pontefract, Ritvo, Archibald, & Murray, 1994). MS patients report that excessive fatigue is a primary factor in their inability to retain previous work schedules or maintain employment (Edgley, Sullivan, & Dehoux, 1991; Jackson, Quaal, & Reeves, 1991; Smith & Arnett, 2005). Fatigue in MS can result directly from disease processes in the brain (termed "primary" or "central" fatigue) or indirectly from symptoms commonly experienced in MS, such as physical disability, sleep

disturbance, an increase in body temperature, or depression (termed "secondary" or "peripheral" fatigue; Johnson, 2008; Leavitt & DeLuca, 2010).

A recent study highlighted the interrelatedness of fatigue and depression. Researchers assessed depression, anxiety, and fatigue in 101 MS patients every 3 months for a 2-year period, along with several other variables, including stressors, lifestyle factors, and psychosocial functioning (Brown et al., 2009). They found that anxiety, fatigue, and depression were all highly related. Specifically, baseline depression levels explained most of the variance in anxiety and fatigue scores at the 2-year follow-up. Similarly, early anxiety and fatigue scores explained a significant portion of the variance in later depression scores.

Other research has determined that depression, sleep disturbance, and disease severity are strong predictors of fatigue (Strober & Arnett, 2005). All three variables together account for 43% of the variance in fatigue levels, while depression accounts for 22% of the variance in fatigue. A longitudinal study of 198 MS patients found that fatigue, depression, and anxiety were all present in a large percentage of patients, and over the 2½-year monitoring period, only anxiety decreased over time (Wood et al., 2012). Finally, depression and fatigue have been shown to be correlated with subjective cognitive complaints both before and after CBT to treat depression (Kinsinger et al., 2010). Currently, the cause of the relationship between depression and fatigue in MS is unclear. Additional research is needed to determine potential shared biological pathways through which these processes may manifest in MS.

It can be difficult to distinguish fatigue related to MS processes from depression-related fatigue. Clinicians have reported that, in general, the fatigue of MS is reduced in the morning, and patients often improve with sleep or a rest break. In contrast, the fatigue of depression is more likely to be worse in the morning and does not respond to rest (Krupp & Pollina, 1996). Clinicians can use two self-report measures that are recommended for assessing fatigue with MS patients: the Fatigue Impact Scale and the Fatigue Severity Scale. The Fatigue Impact Scale is a 21-item tool that measures the influence of fatigue on daily life; scores on this measure have been shown to be a significant predictor of mental health and overall physical health for MS patients (Fisk et al., 1994). The Fatigue Severity Scale is a nine-item measure developed for assessing the severity of fatigue in MS and has shown good reliability (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989). It is recommended that clinicians assess fatigue using these tools on a routine basis in order to identify patients who are experiencing excessive fatigue in their daily lives.

Management of fatigue can involve multiple approaches (Krupp, Serafin, & Christodoulou, 2010). For instance, a recommended approach involves treating any underlying factors that might be contributing to secondary fatigue, such as disturbed sleep or depressed mood. Exercise has also been supported as a method of reducing fatigue (McCullagh et al., 2008). In contrast, there is only mixed support for the efficacy of pharmacotherapy agents such as amantadine (Pucchi et al., 2007) and modafinil (Brown, Howard, & Kemp, 2010).

COGNITIVE DEFICITS

Between 40% and 65% of MS patients experience cognitive difficulties associated with the disease (Chiaravalloti & DeLuca, 2008; Rao et al., 1991a; Winkelmann, Engel, Apel, & Zeitl, 2007). Deficits have been documented in several domains of cognitive functioning, including memory, attention, visuoconstruction ability, information processing speed, and cognitive flexibility (Chiaravalloti & DeLuca, 2008; Winkelmann et al., 2007). Cognitive decline is associated with a variety of real-world difficulties in MS, including problems managing independent activities of daily living, problems in social relationships, difficulty maintaining adherence to medications, difficulty driving, and maintaining employment (Benedict et al., 2005; Bruce et al., 2010; Higginson, Arnett, & Voss, 2000; Rao et al., 1991b).

Depression is associated with several cognitive problems in MS. Depression is related to objectively measured deficits in the areas of speeded attention, working memory, and planning (Arnett et al., 1999a, 1999b, 2002). Older studies frequently failed to find relationships between cognitive problems and depression in MS (Feinstein, 2006). However, more recent studies improved on the methodology of earlier attempts and have documented a relationship between depression and cognitive problems in MS (Arnett et al., 2008). Arnett and colleagues suggested that inconsistent findings could be due in part to the presence of a moderator variable that was not being consistently measured. Studies have since found that depression is related to cognitive dysfunction for MS patients who use maladaptive coping strategies; depression is not related to cognition among MS patients who use

adaptive coping strategies (Arnett, Higginson, Voss, & Randolph, 2002; Rabinowitz & Arnett, 2009). These findings suggest that teaching adaptive coping strategies to patients with cognitive difficulties may decrease the likelihood of subsequent depressive episodes.

BRAIN CHANGES

Disease activity in the brains of MS patients typically takes the form of inflammation and demyelination in white matter supporting the cerebral cortex (Bø, Vedeler, Nyland, Trapp, & Mørk, 2003). The exact pattern and location of damage vary from patient to patient. Imaging studies demonstrate a relationship between structural brain changes and depression in MS. Among other areas, depression is associated with the presence of an increased number of hypointense lesions (Bakshi et al., 2000), higher lesion volume in the left medial inferior frontal region (Feinstein, Roy, Lobaugh, Feinstein, & O'Connor, 2004), increased gray matter atrophy in left anterior temporal regions (Feinstein et al., 2004), and more hippocampal atrophy. In fact, lesion burden in the left medial inferior frontal region and atrophy in the left anterior temporal region together predicted 42% of the variance in the presence of major depression. As Feinstein (2011) points out in a recent review article, most imaging studies to date have been investigations of structural correlates of depression, and little attention has been paid to the use of functional MRI. Examining the association between depression and functional MRI may be useful to determine whether functional differences exist between depressed and non-depressed MS patients, and whether specific treatments produce a change in functionality.

PERSONALITY CHANGES

MS patients frequently experience personality changes (Stathopoulou, Christopoulos, Soubasi, & Gourzis, 2010). Reported changes include disinhibition, apathy, increased irritability and impulsivity, as well as emotional lability (Stathopoulou et al., 2010). As with many other side effects of MS, these changes vary significantly between patients and have the potential to produce strain on interpersonal relationships. Psychopathology has been shown to be related to personality dysfunction in MS patients, with depressed or anxious patients showing greater neuroticism, less extroversion, less agreeableness, and less conscientiousness than non-depressed and nonanxious MS patients (Bruce & Lynch, 2011). A cognitive-behavioral intervention focused on social skills training and behavior modification has shown some promise in improving social behavior in MS patients with personality or behavior disorders (Benedict et al., 2000). This small single-blind trial provided education regarding common personality and cognitive symptoms of MS, as well as methods to cope with these difficulties to patients and their caregivers. Additional research including interpersonal therapy is encouraged in order to further pinpoint nonpharmacological interventions that address personality and social difficulties that may arise during the treatment of depression in MS.

SIDE EFFECTS OF DMTS

Administration of both interferon-α and interferon-β have been shown to be related to depression among patients with a history of mood disturbance, in both MS and non-MS patient groups (Feinstein, O'Connor, & Feinstein, 2002; Lotrich, 2009; Sockalingam & Abbey, 2009). However, a recent case series has suggested that severe depression in some MS patients might be caused by a rare adverse event related to use of interferon-β, a DMT frequently prescribed to treat MS (Fragroso et al., 2010). The study reported on data from a small number of cases whereby patients developed severe depression and other mood symptoms and attempted suicide while on interferon-β. These patients had no previous history of psychiatric diagnoses. Depressive symptoms abated when interferon-β was stopped. These results have not been replicated elsewhere in the published literature. This study is limited by a small sample size ($N = 11$), so the results should be interpreted with caution. Also, it should be noted that in some instances DMTs may actually help prevent depression, because they are designed to prevent exacerbations and slow the progression of the disease (Kappos et al., 2006). DMTs prevent further inflammation and lesions in the brain, as well as preserving current level of disability and quality of life, just some of the factors associated with depression in MS. The majority of research on the relationship between depressive symptoms and DMT indicate that administration of DMT will help prevent depression, but the relationship is complex.

A Recommended Model for Understanding Depression in MS

Arnett and colleagues (2008) recently published a proposed model for understanding depression in MS, in light of the

myriad of potentially confounding factors already described. Their complex, comprehensive model details how multiple factors can alter a MS patient's lifetime risk of developing depression, which begins with diagnosis of the disease. The disease causes immunological and neurological changes that contribute to the pathogenesis of depression in MS. Additionally, the authors assert that conceptions of self and illness, social support, coping, and stress all moderate the relationship between depression and common sequelae found in MS. These sequelae include physical disability, fatigue, cognitive dysfunction, and pain. These moderator variables can have either an adaptive or maladaptive influence on the patient. When moderator variables are adaptive (e.g., the patient has good support and coping skills), the result is a decrease in the likelihood of depression occurring. When moderator variables are maladaptive (e.g., the patient has poor support and coping skills), the result is an increase in the likelihood of depression occurring in the patient. The authors note that their model is only partially supported by the current literature and encourage future research to test hypotheses derived from their model.

Clinical Guidelines for Practitioners

Perhaps the most important piece of information for a clinician to consider when treating a patient with MS is that proper clinical interview and assessment of symptoms are key. Symptoms commonly seen in cases of depression could be attributed to either clinical depression or MS-related disease processes. In our opinion, the best way to ensure an accurate diagnosis is by conducting a thorough face-to-face clinical interview coupled with the use of assessment tools that are specifically recommended for use in screening for depressive symptoms in MS patients (e.g., BDI-FS and CMDI).

Once clinically definite depression has been diagnosed in MS patients, a clinician can apply one of several evidence-based treatments to successfully relieve symptoms. Evidence supports the use of in-person and telephone-administered CBT, group therapy, antidepressant medications (e.g., see Koch, Glazenborg, Uyttenboogaart, Mostert, & De Keyser, 2011), therapy combined with antidepressants, and mindfulness training. Clinicians can access a provider and patient manual specifically designed for treating depression in MS patients in the Oxford University Press *Treatments That Work* series.

Clinicians are encouraged to advocate for their MS patients with other treatment providers and participate in the patient's multidisciplinary team. Frequently, significant others and caregivers should be invited to be involved in the treatment process. Successful treatment of depression in MS patients is achievable and has the potential to produce other positive effects for patients, including increased adherence to DMTs, decreased fatigue, improved overall quality of life, and decreased complaints of cognitive problems. Finally, we urge clinicians to closely monitor MS patients and offer booster sessions if needed following treatment. Given the fact that many people with the disease experience symptoms that can suddenly appear and then suddenly remit, patients may benefit from ongoing emotional support and coping skills retraining.

Summary and Conclusions

MS is a chronic disease that affects the central nervous system and can cause a wide variety of both physical and cognitive deficits. Approximately 150 people in every 100,000 are living with the disease in the United States. Depression is commonly found among this population, with as many as 50% of patients receiving a diagnosis of major depression during their lifetime. Comorbid depression in MS presents clinicians with unique challenges, as it is often difficult to distinguish from common symptoms of MS and can be associated with several other signs of neurological disease.

Research has established that the BDI-FS and CMDI's mood and evaluative subscales can aid clinicians in the accurate diagnosis of depression in MS. Additionally, several studies have determined that CBT, pharmacotherapy, and mindfulness-based interventions are effective in treating depression in MS. A CBT-based intervention specifically designed for MS patients has been validated and published in a treatment manual for clinicians and associated workbook for patients. These are available to clinicians in paperback from major retailers. Therefore, despite the challenges of accurate screening and diagnosis, the clinician has options available to successfully treat depression in MS.

Future studies can expand upon the existing literature in a number of ways. For instance, further

examination of the efficacy of other psychotherapy approaches is warranted, including techniques such as behavioral activation. Further, exploration into alternative methods of treatment, such as structured exercise, yoga, or light therapy, would yield valuable information about the treatment of depression and perhaps other associated factors in MS (e.g., improvements in cognitive deficits or fatigue). Although treatment works for 29%–57% of patients, there are still a significant number of patients for whom treatment does not appear to reduce depressive symptoms. Therefore, examining other modes of treatment will be vital in addressing the need for depression treatment in MS. Trials in which other therapy approaches are compared with already recommended treatments in MS (e.g., CBT) would particularly enhance this body of literature. Researchers should incorporate the recommended self-report measures (BDI-FS and subscales of the CMDI), rather than relying on measures that fail to account for the unique presentation of depression in MS. Future research should also focus on optimizing treatment by combining beneficial strategies with known benefits, such as the comparison of pharmacotherapy agents, and pharmacotherapy combined with psychotherapy. Further research is also needed to find appropriate screening tools for assessing suicide risk, since no suicide screening tools have been validated for use with MS patients. Clinicians would undoubtedly benefit from having such a measure to assist in accurately detecting MS patients at risk for suicide.

In conclusion, clinicians need to be aware of the complex picture of depression in MS, and take the necessary steps to accurately recognize depression and offer validated treatments. Successful treatment of depression in MS is achievable. There is evidence that depression in MS can be effectively treated with CBT and pharmacotherapies. Treating depression in MS has far-reaching effects on the lives of MS patients. Reprieve from symptoms of depression not only improves mood and quality of life for MS patients, but also adherence to DMT and, as a result, may slow disease progression in the brain.

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CHAPTER

24 HIV/AIDS and Depression

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Abstract

Depression is highly prevalent among individuals living with HIV/AIDS. Depression not only affects quality of life for this population but also confers significant barriers to optimizing self-care behaviors, which are essential to medical care. Two of the most important HIV/AIDS care behaviors are medication adherence and safe sex practices; inadequacy in both can be associated with depression. Depression among those living with HIV/AIDS also is associated with substance abuse, which in turn predicts poor self-care. Importantly, there has recently been an emphasis on creating and testing integrative psychosocial interventions that address depression and self-care behaviors among people living with HIV/AIDS. These combination treatments have displayed initial efficacy and appear to be efficient in addressing multiple health behaviors. This chapter briefly reviews the epidemiology of HIV/AIDS and salient biological outcomes in the context of depression. It then discusses the role of depression and self-care behaviors and it concludes with a review of interventions and future research priorities.

Key Words: HIV/AIDS, depression, safe sex practices, adherence, psychosocial interventions, self-care behaviors

Introduction

HIV/AIDS continues to be a highly prevalent major public health concern in the United States, with depression being one of the most frequently occurring comorbid conditions. Depression, as a comorbidity to HIV/AIDS, is important not only in that it affects the quality of life for those living with the virus but also because of its complex association with various self-care behaviors important to living with HIV and maximizing the potential benefits of HIV treatment. Two of these important self-care behaviors are adherence to antiretroviral therapy (ART) medications, which is required to attain a suppressed viral load; and safer sexual practices to reduce HIV transmission to sexual partners and avert potential complications such as acquisition of sexually transmitted infections. Depressive symptoms also augment the risk of substance use to manage distress. The present chapter reviews these issues in the following ways. First, we outline the epidemiology of HIV/AIDS in the United States. Next, we review relevant biological outcomes and ART medication adherence among HIV-infected individuals in the context of comorbid depression. Third, we discuss the impact of depression on HIV sexual transmission risk, injection drug use, and quality of life. Fourth, we review the role of depression in treatment utilization and behavioral models of HIV transmission risk. Finally, we discuss treatments for depression specific to HIV-infected individuals and comment on future directions and research priorities.

Epidemiology of HIV/AIDS in the United States and Its Association with Comorbid Depression

Despite educational and prevention efforts, the number of annual incident HIV cases in the United States has remained stable over the past

10 years (CDC, 2011a). Nearly 50,000 individuals living in the United States were infected with HIV in the last available reporting period, 2009 (Prejean et al., 2011). These individuals joined the more than 1.1 million estimated to be living with HIV in the United States as of 2008 (CDC, 2011a). African Americans and men who have sex with men (MSM) represent the vast majority of both new infections and those living with the disease (CDC, 2010; Hall et al., 2008). It should be noted that "MSM" is a classification used within the HIV literature to describe sexual risk behavior rather than sexual identification (e.g., "gay or bisexual men"), as sexual behavior and self-identification do not necessarily overlap. Indeed, more than half of all incident infections are among MSM, with male-to-male sexual contact accounting for 57% of new infections in 2009 (CDC, 2011a). The incidence rate is comparable among African Americans, also comprising nearly half of all new infections in 2009 (Prejean et al., 2011). Disproportionate numbers of African American women in particular are impacted by the disease; they are 15 times more likely than white women and 4 times more likely than Hispanic women to be infected with HIV (CDC, 2011b; Hall et al., 2008). Intravenous drug use (IDU) also constitutes a major risk factor for contracting HIV. It is estimated that nearly 10% of all incident HIV infections in 2009 were attributable to IDU and that, since the epidemic began, 36% of all HIV cases in the United States have been attributed to IDU (CDC, 2007; 2011c).

Although the number of individuals contracting HIV has remained steady in recent years, the mortality rate from HIV has declined significantly (Crum et al., 2006). The advent of ART in the late 1990s transformed HIV from a fatal disease into a chronic, manageable condition in settings with the resources for treatment. Despite the great strides made in diagnosing and treating the infection, however, many individuals living with HIV still face a multitude of illness-related challenges. These can include maintaining excellent adherence to medications, facing potential stigma related to the infection, potential side effects of medications, and negotiating important quality-of-life behaviors such as engaging in sexual relationships (for a review see Psaros, Israel, O'Cleirigh, Bedoya, & Safren, 2011). The cumulative stress of such challenges is one pathway toward impacting the mental health of those living with HIV.

Importantly, depression is one of the most common comorbidities with HIV/AIDS. The best available empirical data estimate that up to 36% of those living with HIV suffer from comorbid depression (Asch et al., 2003; Bing et al., 2001). Bing et al. compared rates of depression among HIV-infected individuals to a nationally representative uninfected reference group (Substance Abuse and Mental Health Services Administration, 1996) in which the prevalence rate of depression was 7.6%, a rate nearly five times lower than that of the HIV-infected sample. This highly disproportionate prevalence of depression among HIV-infected individuals merits heightened awareness of depressive symptoms by healthcare providers as well as careful assessment.

It is important to note that diagnosing depression in those living with HIV can be challenging owing to the overlapping constellation of symptoms that HIV and depression share. A number of somatic symptoms of depression overlap with those of chronic illness and HIV, including loss of energy, trouble concentrating, and decreased appetite and/or weight loss (Kalichman, Rompa, & Cage, 2000; Simoni et al., 2010). Accordingly, some have suggested that cognitive and mood symptoms (e.g., guilt, hopelessness, anhedonia) should be weighed more heavily than somatic symptoms (e.g., fatigue, diminished appetite, and sleep disturbances) by a provider in determining if a particular patient living with HIV is clinically depressed (e.g., Kalichman, Rompa, & Cage, 2000). Furthermore, there is evidence that depression among those living with HIV is likely underdiagnosed by providers in clinical care settings (e.g., Asch et al., 2003). In addition, in some cultural settings depression symptoms are generally more somatic; so one should not rule out potential depression when somatic symptoms are present. As the following sections illustrate, failing to identify and properly treat depression in HIV-infected individuals can have significant ramifications not only for patients' mental health but also their physical health and self-care abilities.

Biological Indicators of HIV Outcomes: Viral Load, CD4 Count, and Progression to AIDS

The treatment for HIV, ART, is a combination therapy of at least three antiretroviral drugs that act to impede viral replication and thus suppress the levels of the HIV virus in the body, also known as the "viral load." If the virus is suppressed, it is no longer able to weaken the immune system. A consequence of uncontrolled virus, however, is the gradual decline in immune functioning, which can be measured by the quantity of T-cell lymphocytes,

or CD4 cells, in the bloodstream. HIV depletes these "helper cells," which are crucial for properly fighting pathogens; this weakens the immune system and causes the individual to become susceptible to secondary diseases and infections (opportunistic infections). The HIV virus progresses to AIDS if a person's CD4 count drops below 200 or if certain opportunistic infections (e.g., candidiasis, cytomegalovirus, and Kaposi's sarcoma) are present (CDC, 2008). At this stage of the disease, individuals are much more highly susceptible to such infections, which can be fatal.

Adherence to ART and HIV Outcomes

Although ART has revolutionized HIV treatment, high levels of adherence are required to reap therapeutic benefits. In the first set of ART regimens, typically, 95% adherence was considered necessary to achieve optimal health outcomes such as undetectable viral load, high CD4 values, fewer HIV symptoms, and lower rates of hospitalization (Low-Beer, Yip, O'Shaughnessy, Hogg, & Montaner, 2000; Paterson et al., 2000). Although newer ART drugs—such as nonnucleoside reverse transcriptase inhibitors (NNRTIs) and boosted protease inhibitors (boosted PIs)—may be more forgiving with regard to occasional missed doses (Kobin & Sheth, 2011; Martin et al., 2008), suboptimal adherence significantly undermines the efficacy of ART and increases patients' risk for corresponding adverse medical outcomes. It is essential that HIV-infected individuals on ART work toward consistent and sustained adherence, as it has been suggested that even occasional and temporary lapses can negatively impact physical health and can do so well into the future (e.g., Li et al., 2005).

Depression and Nonadherence

The detrimental effect of depression on medication adherence among those living with HIV is well established in the scientific literature. A recent meta-analysis from our group identified 95 studies focused on the association between depression and nonadherence in HIV; it showed that those with depression were significantly less adherent to their medication regimens than those without (r = .19; Gonzalez, Batchelder, Psaros, & Safren, 2011a). Moreover, there was an incremental relationship between depressive symptoms and adherence, with degree of depressive symptoms negatively associated with increases in adherence. This also extends to initiation or retention in medication treatment. For example, Tegger and colleagues (2008) found that individuals with depression who were not already on a stable medication regimen were much less likely to initiate ART treatment and took longer to do so than those who were similarly newly eligible for ART but not depressed. Further, Carrico et al. (2011) found that individuals reporting greater numbers of depressive symptoms at baseline were 39% more likely to discontinue ART by follow-up, even after controlling for associated factors such as baseline adherence score. The impact of depression on ART adherence has been discerned clearly by Kacanek et al. (2010), who determined that the onset of depression was temporally linked to the development of consequent suboptimal adherence. In that longitudinal study, individuals who were not depressed at baseline but developed depression by follow-up had significantly lower rates of adherence after depression onset compared with those who did not enter into a depressive episode. Importantly, rates of adherence at baseline were identical among those who became depressed and those who did not. The onset of depression impairing subsequent ART adherence underscores the deleterious effects of depression on self-care and disease management among HIV-infected individuals.

Although the relationship between depression and nonadherence has been clearly established, the mechanisms that drive the relationship remain somewhat unclear. Cognitive behavioral theories of depression, however, have aided in formulating explanatory models. For example, core depressive symptoms such as feelings of worthlessness, hopelessness, loss of interest, concentration problems, and negative thoughts about one's self and the future can serve as obstacles to the self-care behaviors required for optimal health outcomes and disease management (see Rabkin, 2008). In addition, the presence of somatic depressive symptoms, such as diminished appetite, can also act as direct obstacles to antiretroviral adherence—for example, if patients have been instructed to take medications with meals or experience adverse gastrointestinal side effects (e.g., Gonzalez et al., 2011b). The array of logistical, psychological, and physiological barriers to taking ART confers significant challenges to adherence among HIV-infected individuals living with comorbid depression. For this population, depressive symptoms can significantly hinder adherence to a drug therapy that is already difficult to manage.

Depression and Health Outcomes

Given the consistent link between depression and ART nonadherence, it is not surprising that

there is a documented association between depression and negative health outcomes. Individuals endorsing depressive symptoms have been shown to experience declines in their CD4+ cell counts, increased viral loads, faster progression of HIV illness, and more HIV-related symptoms over time than those without depressive symptoms (Carrico et al., 2011; Cook et al., 2002; Ickovics et al., 2001; Ironson et al., 2005; Leserman, 2008; Li et al., 2005; Patterson, Shaw, Semple, & Cherner, 1996; Pence, Miller, Gaynes, & Eron, 2007). For example, Carrico et al. (2011) found a 50% higher mean viral load among those endorsing a greater number of depressive symptoms at baseline. Similarly, individuals suffering from chronic or even intermittent depressive symptoms over a seven-year period were found to have significantly greater declines in their CD4 cell counts compared with individuals without such symptoms (Ickovics et al., 2001). This association remained even after controlling for ART use and adherence, indicating that inconsistent adherence only partially mediated this effect.

Unfortunately HIV virus replication and corresponding immune suppression can have devastating consequences for patients, with biological markers of HIV progression translating into worse clinical outcomes as well. Therefore depressed patients are at risk for faster all-cause and HIV-related mortality from opportunistic infections compared with those without depression (Antelman et al., 2007; Cook et al., 2004; Ickovics et al., 2001; Leserman et al., 2007; Lima et al., 2007). For example, depression was linked to disease progression and mortality over a six- to eight-year period following HIV diagnosis among 996 women living in Sub-Saharan Africa (Antelman et al., 2007) even when accounting for initial disease severity. Those who were depressed were 60% more likely to have progressed to an advanced stage of the disease and more than twice as likely to die as those who were not depressed. Studies exploring the link between depression and HIV-related mortality have yielded similar results. Women who exhibited chronic depressive symptoms over 7 to 7.5 years had more than double the HIV-related mortality as women without these symptoms, again when controlling for factors such as baseline CD4 cell count and the mediating effects of medication adherence (Cook et al., 2004; Ickovics et al., 2001).

Although there is evidence that nonadherence is one mediator in the relationship between depression and negative health outcomes among those with HIV (Carrico et al., 2011), the link between depression and mortality beyond the effects of adherence suggests that other factors may also account for the negative impact of depression on medical outcomes (Leserman, 2008). Specifically there is some evidence that biological mechanisms in the central and sympathetic nervous systems are partly responsible for the association between depression and disease progression. Although the exact mechanisms are not yet fully understood, studies suggest that psychological stress and depression can have adverse effects on immune response by disrupting chemical pathways in the brain (Leserman et al., 2002, 2007). Stress and depression have been linked to chronically increased levels of the hormones cortisol and norepinephrine, both of which, in turn, have also been associated with decreased immune functioning and more rapid HIV disease progression (for a review see Leserman, 2003). Given the potential role of these stress hormones in furthering HIV disease, psychological interventions that provide skills for coping and stress management (for a review of such interventions see Carrico & Antoni, 2008) may be integral in mitigating the detrimental effects of depression and stress on the immune system and minimizing the potential for subsequent, undesirable health outcomes.

Behaviors Risking Sexual Transmission

Theoretically, depression has been associated with sexual behavior linked with the risk of HIV transmission, such as unprotected anal or vaginal intercourse with serodiscordant (i.e., having a different HIV status) or unknown-status partners. It has been argued that individuals who experience depression may search for means to escape this unpleasant affective experience. One such escape behavior may be engaging in unprotected sex. Another pathway of depression to sexual risk taking is through maladaptive cognitions, which are common among individuals who are depressed (e.g., Beck, 1972). Given that self-efficacy, or the belief in one's ability to successfully complete a task when needed (e.g., believing that one has the ability/skills to use a condom during sexual intercourse) is associated with the behavior of practicing safer sex, this may be a particularly vulnerable pathway for depressed individuals. For instance, depressed individuals often view themselves negatively and have low confidence in their ability to successfully achieve difficult acts (e.g., Kavanagh & Bower, 1985). Empirically, elevated levels of depression have been linked to sexual risk taking (e.g., Bradley, Remien, & Dolezal, 2008; Koblin et al., 2006; Ryan, Forehand, Solomon, &

Miller, 2008; Stall et al., 2003). Alternatively, it is also possible that for some people, depression may be inversely related to sexual risk. Individuals who are depressed tend to generally be more aware of risky situations and more likely to be cautious in making decisions in regard to these potentially hazardous predicaments (e.g., Pietromonaco & Rook, 1987; Schwarz, 1990). In fact, depressed individuals typically view neutral situations as more risky than do nondepressed individuals (e.g., Johnson and Tversky, 1983). Additionally, when depression reaches high levels, decreased sexual libido may be present (e.g., Baldwin, 2001; Mao et al., 2009; Schreiner-Engel & Schiavi, 1986), which in turn suggests a lower probability of engaging in any sexual encounters (risky or otherwise). Empirically, the results of a meta-analysis (Crepaz & Marks, 2001) revealed a modest, nonsignificant relationship (r = .04) between depression and sexual risk behaviors. However, it should be noted that there was significant heterogeneity among the various effect sizes. This suggests the presence of unaccounted moderator variables, which was noted by the authors as well as by Kalichman and Weinhardt's (2001) critique. Indeed, it is quite possible that depression is related to sexual risk behaviors for some groups of individuals but not others.

One potential reason for some studies showing an association of depression to sexual risk and others not may be due to the nature of the potential relationship. Most studies examine linear effects. When nonlinear relationships have been examined, results have indicated that moderately elevated levels of depression are related to increased HIV sexual transmission risk among HIV-uninfected (Koblin et al., 2006) and HIV-infected (O'Cleirigh et al., 2011) MSM. This would be consistent with the symptom of loss of libido potentially being increasingly prevalent among those with higher levels of depression severity. Additional research with HIV-infected MSM has revealed conditions under which depression is a significant predictor of sexual risk. For example, body mass index (BMI) moderates this relationship, with underweight depressed MSM being more likely to engage in sexual transmission risk behaviors (Blashill, O'Cleirigh, Mayer, Goshe, & Safren, 2012).

In sum, the relationship between depression and HIV sexual transmission risk behaviors remains unclear. In examining bivariate, linear relationships, nonsignificant associations are frequently noted. However, when curvilinear or moderation analyses are conducted, a more nuanced perspective is gleaned, with associations of sexual risk to mild or moderate levels of depression. Going forward, researchers should be advised not to rely solely on linear models and should also consider possible interactive variables as well as proposing mechanistic (i.e., mediational) pathways between depression and sexual risk behavior.

Injection Drug Use

Injection drug use (IDU) is related to both depression and HIV transmission risk. Like sexual risk behaviors, IDU tends to occur within a psychosocial context. For instance, depressive disorders are commonly found among opiate and stimulant abusers (e.g., Berger-Greenstein et al., 2007; Brienza et al., 2000). Theoretically, depression has been viewed as an internal trigger for drug craving (McLellan, Luborsky, Woody, O'Brien, & Druley, 1983). Similarly, the existing empirical literature to date also highlights the association between depression and IDU (e.g., Latkin et al., 2008; Metzger et al., 1991; Stein, Solomon, Herman, Anderson, & Miller, 2003).

Early research has revealed differences between IDU and non-IDU in regard to levels of depression as well as relevant within-group differences in regard to the association of depression to HIV risk. For example, Metzger et al. (1991) compared IDU who shared needles with IDU who did not share needles as well as with a non-IDU group. The authors examined several demographic and psychosocial variables and results revealed that IDU who shared needles reported significantly higher levels of depression compared with IDU who did not share and non-IDU (the latter two groups did not differ). These findings suggest that depression may be related to needle sharing, which is a highly important factor in regard to HIV prevention.

Additional research has yielded similar results, with findings revealing nonsignificant associations between the frequency of IDU and depression (Stein et al., 2003) but also indicating significant associations between depression and the sharing of injection equipment (odds ratios range from 1.34 to 1.53; Latkin et al., 2008; Stein et al., 2003). These results point to direct associations of depression to needle sharing, versus IDU per se, which is a highly risky behavior potentiating HIV spread. Conceptually, elevated levels of depression may lead to hopelessness, which in turn may predict poor self-care behavior, in this context, the sharing of needles. Cognitive factors such as a negative or pessimistic view of the world, future, and self may also

contribute to decreased motivation to practice safer behaviors in the context of using injection drugs (e.g., utilizing needle exchange if available, using bleach to clean needles). As with the literature on depression and sexual transmission risk behaviors, more sophisticated models are needed that explore both mediating and moderating factors.

Other Common Substances: Methamphetamine (Crystal Meth) and Alcohol

Tantamount to the risk of HIV transmission implicit within IDU are analogous risks accompanying methamphetamine (meth) use, including sexual risk transmission behavior and suboptimal medication adherence. Meth use is common, as nearly 70% of HIV-infected MSM and 64% of heterosexual HIV-infected men in one study reported lifetime use (Marquez, Mitchell, Hare, John, & Klausner, 2009). Further, meth use and depression are interrelated. HIV-infected meth users in one study reported initiating meth usage as means of coping with HIV-related depression (Robinson & Rempel, 2006), and meth has also been implicated in promoting self-treatment of anhedonia and negative affect that occur following episodes of use (Glasner-Edwards et al., 2009; Kurtz, 2005; Mimiaga et al., 2008; Newton, Kalechstein, Duran, Vansluis & Ling, 2004; Zweben et al., 2004). Importantly, meth use has been linked with sexual transmission risk, with motivations for use largely involving the enhancement of sexual appetite and pleasure derived from sexual activity (e.g., Reback, Larkins, & Shoptaw, 2004; Semple, Patterson, Grant, 2002). Meth-using MSM have been shown to have a higher number of sexual partners and episodes of unprotected sex than those who did not use meth (e.g., Halkitis, Parsons, Stirratt, 2001; Halkitis, Shrem, Martin, 2005; Semple et al., 2002). Furthermore, episodes of meth use are often concomitant with periods of ART nonadherence (Marquez, Mitchell, Hare, John, & Klausner, 2009; Reback, Larkins, & Shoptaw, 2003). Such lapses may be unplanned (e.g., due to disrupted schedules or appetite disturbances) or planned lapses motivated by a primary interest in sexual enjoyment, liberation, and "feeling alive" (e.g., Reback, Larkins, & Shoptaw, 2003). As discussed previously, even these episodic interruptions in ART medications can have lasting complications for HIV treatment, rendering meth use an important concern in the context of HIV treatment and self-care.

Disruption to treatment and self-care regimens also constitutes a significant concern for HIV-infected individuals who abuse alcohol. Alcohol is commonly abused among this population, with one study finding rates of heavy drinking nearly double those found in the general population (Galvan et al., 2002). Furthermore, elevated depressive symptoms have been directly associated with increased levels of alcohol use among those living with HIV (e.g., Ghebremichael et al., 2009; Sullivan et al., 2008; Velasquez, von Sternberg, Johnson, Green, Carbonari, & Parsons, 2009). While more research is needed to explicate the direction of causality between depression and alcohol use among HIV-infected individuals, substantial literature in the general population suggests that alcohol may be utilized as a coping mechanism to self-medicate negative affect (for recent meta-analyses and reviews, see Conner, Pinquart, & Gamble, 2009, and Thornton et al., 2012). Alternatively, some research studies noted in these reviews suggest that level of drinking impacts depressive symptoms, such that individuals who increase or decrease their alcohol use experience higher and lower levels, respectively, of depressive symptoms after the switch. Thus the relationship between alcohol use and depressive symptoms may be cyclical and intricately interconnected rather than exclusively causal in either direction.

With regard to HIV self-care, alcohol use among HIV-infected individuals has been related to increased instances of unprotected sex (for a meta-analysis, see Shuper, Joharchi, Irving, & Rehm, 2009). In the context of depression, there is evidence that negative affect may moderate this effect, with higher depressive symptoms strengthening the correlation between alcohol use and unsafe sex (Barta, Tennen, & Kiene, 2010). Alcohol use has also been widely cited as detrimental to medication adherence among HIV-infected individuals (Azar, Springer, Meyer, & Altice, 2010; Hendershot, Stoner, Pantalone, & Simoni, 2009). Kalichman et al. (2009) suggest that such nonadherence may be due to the common belief that drinking alcohol while taking medications can have toxic effects. While few studies thus far have studied the relationship between alcohol abuse and nonadherence specifically among individuals living with both depression and HIV, these findings, coupled with the high rate of alcohol abuse among those living with HIV, underscore the need for attention to alcohol use as an obstacle to medication adherence and corresponding health benefits.

Quality of Life

Depression generates significant impairment in physical, social, and role functioning, conferring

many negative effects on quality of life (Schonfeld et al., 1997) over and above quality-of-life impairments stemming from a chronic medical condition (Wells et al., 1989). For those living with a chronic medical condition as well as clinical depression, well-being and quality of life may be doubly disrupted (e.g., Wells et al., 1989). First, individuals living with HIV may experience worse health-related quality of life due to pain and other symptoms related to the HIV infection (Briongos-Figuero, Bachiller-Luque, Palacios-Martín, González-Sagrado, & Eiros-Bouza, 2011; Patel et al., 2009; Schag, Ganz, Kahn, & Petersen, 1992). For example, in one large study across resource-constrained and resource-rich settings (Safren et al., 2011), there was evidence that individuals with lower CD4 counts experienced worse social, cognitive, and physical functioning compared with those with higher levels of CD4 cells. Moreover, those with lower CD4 counts also reported more pain, less energy, and worse general perceptions of their own health.

In addition to the effects of poor medical outcomes on well-being, HIV-infected individuals living with depression must also cope with impairment related to depression itself. Individuals with comorbid HIV and depression experience worse quality of life than those who are HIV-infected but not depressed, living with poorer physical and mental health beyond the effects of disease progression (Liu et al., 2006; O'Cleirigh & Safren, 2006; Sherbourne et al., 2000). In one recent study, Briongos-Figuero et al. (2011) found that individuals with HIV who were depressed scored lower in every domain of health-related quality of life compared with their nondepressed counterparts, including physical, role, social functioning, general health perceptions, energy, cognitive functioning, and overall mental and physical health. For individuals coping with both HIV and depression, the collective symptoms and challenges implicit within each illness can be immense. Such individuals may experience extensive and often debilitating deficits in quality of life and well-being—deficits above and beyond the adverse influence of HIV or depression alone.

Treatment Utilization

Cutting across chronic medical illnesses, comorbid depression is associated with roughly a 50% increase in medical costs, even when controlling for severity of the medical condition (e.g., Katon, 2003). Specific to HIV, depression has been identified as the second leading factor predicting hospitalizations (Marimoutou et al., 2003). Furthermore, HIV-infected individuals who were depressed and treated with an antidepressant accounted for significantly lower total medical expenditures compared with their nontreated counterparts (Sambamoorthi, Walkup, Olfson, & Crystal, 2000).

In our group's own work, we recently showed that elevated depressive symptoms were associated with increased health care utilization (O'Cleirigh, Skeer, Mayer, & Safren, 2009). Importantly, these findings controlled for disease stage, demographic characteristics, and ART adherence. Thus it appears that depression is a salient factor in regard to increased health care utilization among HIV-infected individuals, likely amplifying both costs to the patient as well as strain on government-funded sources of health care.

Depression May Interfere with Existing Models of Behavioral Change in Those with HIV

Depression may also call into question some of the assumptions underlying existing theoretical models of behavior change. Almost all models of HIV transmission risk behavior are based on social psychological theories that may not fully consider the impact of strong affective experiences. For instance, one of the most widely applied theories, social-cognitive theory (Bandura, 1994; Wulfert, Safren, Brown, & Wan, 1999; Wulfert, Wan, and Backus, 1996), implicates positive (e.g., reducing HIV and sexually transmitted infections) and negative (e.g., condoms make sex less enjoyable) beliefs as well as perceived social norms in the causal pathway to self-efficacy beliefs concerning safer sex practices. Symptoms or diagnoses of depression may be related both directly to these normative appraisals and indirectly by altering the interrelationships between these factors.

We recently examined the utility of the social-cognitive model of HIV transmission in a sample of HIV-infected MSM, examining the model's fit in those who screened in for clinical depression and those who did not (Safren et al., 2010). In the cognitive theory of depression (Beck, 2008), negative attributions about oneself, others, and the world predominate. These cognitive distortions affect social-cognitive variables and their association with HIV risk. In our analysis, there was good fit between the data and the social-cognitive model for HIV-infected MSM who were not depressed; however, for their depressed counterparts, the data did not fit the model well. For depressed HIV-infected MSM, the mechanism of

the model—self-efficacy—was not associated with HIV transmission risk.

This was the first empirical test of the impact of depression on the hypothesized relationships specified by the underlying sexual behavior change model. These analyses were specifically applied to the social-cognitive model; however, one could test other social psychology models of HIV-related behavior that serve as the basis for individual interventions, such as the information, motivation, and behavioral skills (IMB) model (Fisher & Fisher, 1992), the theory of reasoned action/planned behavior (Ajzen & Fishbein, 1980), or the health belief model (Rosenstock, Strecher, & Becker, 1988). The interference caused by depression in MSM at risk for acquiring or transmitting HIV suggests that existing theoretical models may not yet account for affective states, which may explain this interference.

Psychosocial Interventions for Depression

To date, there have been a handful of psychosocial interventions developed and subsequently tested focusing on depression among HIV-infected populations. Treatments have included both cognitive behavioral therapy (CBT) and interpersonal psychotherapy (IPT). In the first of these studies, Kelly et al. (1993) randomly assigned participants to either eight sessions of group CBT, a time-matched social support group (SSG) therapy, or a control comparison group. Results at postintervention and three-month follow-up revealed that both the CBT and SSG groups demonstrated significant improvement in depressive symptoms compared with the control condition, but significant differences did not emerge between the two active treatment conditions.

In one of the few studies to examine IPT, Markowitz (1995) compared IPT with supportive psychotherapy among a sample of HIV-infected individuals. At posttreatment, participants assigned to the IPT condition reported significantly lower depression scores compared with those in the supportive psychotherapy condition. In a follow-up study, Markowitz, Svartberg, and Swartz (1998) compared IPT, CBT, supportive psychotherapy, and supportive psychotherapy plus imipramine. Results revealed that the IPT and supportive psychotherapy plus impramine groups reported significantly lower depression scores than the CBT and supportive psychotherapy groups. However, it should be noted that it was unclear if the CBT condition included behavioral techniques such as behavioral activation (or if so, how many sessions were devoted to cognitive vs. behavioral interventions). This is an important point, as behavioral activation in its own right has proven to be a highly efficacious intervention for depression (e.g., Dimidjian et al., 2006). Based on these studies, it would appear that there is conflicting evidence (at least among published randomized controlled trials (RCTs) that required elevated symptoms or diagnosis of depression) regarding the efficacy of CBT. However, there is a rich collection of literature regarding HIV-infected populations highlighting the efficacy of CBT for depression in general (e.g., Butler, Chapman, Forman & Beck, 2006; Tolin, 2010) as well as evaluation studies that do not employ randomized designs or RCTs that do not require depression as an inclusion criterion (for a review see Olatunji, Mimiaga, O'Cleirigh & Safren, 2006).

Psychosocial Interventions for Depression and Medication Adherence

Given that depression is highly prevalent among HIV-infected individuals and is associated with disease progression and ART nonadherence, tailored psychosocial interventions are needed to address depression and adherence in this population. In 2009, our group (Safren et al.) published the results of an initial RCT that compared cognitive behavioral therapy for adherence and depression (CBT-AD) vs. an enhanced treatment as usual (ETAU) condition. Both groups received a brief, CBT/problem-solving intervention called Life-Steps aimed at increasing ART adherence (Safren, Otto, & Worth, 1999); the experimental intervention received CBT, which integrated the adherence counseling into a modular treatment for depression. Participants were then assessed at three, six, and twelve-month follow-ups. Results revealed that at three months, participants in the CBT-AD condition reported greater ART adherence and lower depression compared with participants in the ETAU condition. These results were generally maintained at the six- and twelve-month follow-ups. This study was the first RCT that we are aware of to integrate evidence-based psychosocial treatment for depression with an intervention to increase ART adherence.

The CBT-AD intervention was also evaluated via an RCT among an opioid-dependent HIV-infected sample (Safren et al., 2012). Results indicated that the CBT-AD group reported lower depression at posttreatment, and these gains were maintained at six- and twelve-month follow-up compared with the ETAU condition. The CBT-AD

group also reported greater ART adherence during active treatment; however, these gains were not maintained at follow-up. Although viral load did not differ between the two conditions at follow-up assessments, the CBT-AD group had significantly improved CD4 cell counts over time compared with the ETAU condition. Currently our group is conducting a large, multisite, three-arm RCT for depression and adherence, comparing the CBT-AD intervention to informational and supportive psychotherapy (ISP) and an ETAU condition.

Our CBT-AD intervention has recently been culturally adapted to address the needs of individuals living with HIV at the U.S.-Mexico border (Simoni et al., 2011). In a pilot RCT, 40 participants were randomized to either the CBT-AD condition or a treatment-as-usual condition. Results revealed improvement from baseline to postintervention was greater for the CBT-AD arm compared to TAU on two of the three primary outcomes (i.e., self-report depression and ART adherence). This study adds preliminary evidence that CBT-AD can be adapted successfully with diverse populations.

Psychopharmacological Interventions for Depression in HIV

There have also been several studies that examined the impact of antidepressants on depression among HIV-infected samples. The general consensus among these findings is that psychotropic medications appear to be effective at reducing depressive symptoms among this population (e.g., Ferrando & Freyberg, 2008; Olatunji et al., 2006; Rabkin, 2008). Specific agents—such as selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), and psychostimulants—all appear to be more effective than placebo. Moreover, few differences have been noted between the active agents. However, it is important to note that all psychopharmacological interventions for depression should be carefully and consistently supervised by health-care providers. There is a significant possibility of negative drug-drug interactions among patients being treated for medical and psychosocial comorbidities.

It is possible that treating depression can improve one's overall health, possibly owing to improved depression resulting in better adherence. For instance, Coleman, Blashill, Gandhi, Safren, and Freudenreich (2012) noted that HIV-infected patients who were being treated with antidepressants or psychostimulants not only reported significantly reduced depressive symptoms over time but also evidenced significantly reduced viral loads and significantly increased CD4 T-cell counts over time. Tsai et al. (2010) used structural modeling analysis on a sample of 158 homeless and marginally housed persons with HIV and baseline immune (CD4 count less than 350) and depression (Beck Depression Inventory greater than 13) inclusion criteria. In this longitudinal study, those who started antidepressants were more likely to attain viral suppression, start antiretroviral therapy, and have better adherence. These findings are consistent with data from medical record billing showing, generally, that antidepressant use was associated with better adherence (e.g. Horberg et al., 2008; Walkup, Wei, Sambamoorthi, & Crystal, 2008).

Interventions to Prevent Sexual Risk in HIV

Currently there are few interventions that integrate treatment for mental health issues into HIV prevention. As articulated above, the lack of interventions that address mental health problems is problematic owing to the theory that mental health problems moderate the degree to which models for secondary prevention interventions can be effective (e.g., Safren et al., 2010). Further, in a conceptual review of the literature, Sikkema et al. (2010) highlighted the salient role that mental health treatment offers in reducing transmission risk behaviors among HIV-infected individuals.

There is a rich literature of empirically supported CBT interventions for a broad range of mental health problems (Barlow, 2007) that can serve as a base for integrating the treatment of psychosocial problems with HIV prevention interventions. CBT is generally a short-term intervention, with the typical duration of therapy lasting between 12 and 20 sessions, and includes a wide range of empirically supported behavior change techniques. However, these strategies are largely untested in the treatment of comorbid psychopathology that place individuals at increased risk for HIV acquisition or transmission.

There is promising initial work suggesting that CBT strategies may be effectively used to treat comorbid mental health issues to support reductions in sexual risk behavior in MSM. For instance, in our group, we are testing the integration of behavioral activation and HIV risk-reduction interventions in HIV-uninfected MSM who abuse crystal methamphetamine, or "meth" (Mimiaga et al., 2010; 2012). Behavioral activation is an evidence-based mental health treatment for improving mood and

increasing activity. In this context, it involves learning how to reengage with pleasurable, sustainable, non-drug-related activities in life. The hypothesized mechanism of action is that behavioral activation will reengage participants in pleasurable non-drug-use activities (e.g., interests or hobbies that were enjoyable before crystal meth use). Such activities will serve as natural reinforcement for functional behavior, improve depressed mood when not on crystal meth by experiencing increases in pleasure and mastery, and decrease overall distress so that HIV uninfected MSM who abuse crystal meth can better benefit from sexual risk-reduction counseling. We developed and openly field-tested this intervention among HIV uninfected MSM and found it to be feasible, acceptable, and successful at reducing HIV risk behavior, crystal meth use, and depression at the acute postintervention assessment. Moreover, these effects were sustained at six months.

We are also investigating integrating cognitive processing therapy (CPT) (Resick, Monson, & Chard, 2007) to address childhood sexual abuse-related trauma in the context of sexual risk-reduction counseling for use with MSM at risk for HIV (O'Cleirigh, Shipherd, Goshe, & Safren, 2010). Results from a preliminary pilot RCT also demonstrated impressive findings. At the acute outcome assessment, the experimental CPT condition yielded a 72% reduction in HIV sexual transmission risk behaviors compared with the control condition, which resulted in a 26% reduction.

Directions for Future Research

Over the past several years, attention has been given to integrating HIV self-care interventions with traditional CBT treatments. Because ART nonadherence and HIV sexual transmission risk behaviors occur in a psychosocial context, this approach theoretically follows. Empirically, the initial findings from interventions such as CBT-AD have proved efficacious for the treatment of comorbid depression and ART nonadherence (Safren et al., 2009, 2012). However, future research should also attend to dissemination and implementation of these interventions. Further, as is currently being tested in the treatment of depressive and anxiety disorders (e.g., Barlow, Allen, & Choate, 2004; Ellard, Fairholme, Boisseau, Farchione, & Barlow, 2010; Wilamowska et al., 2010), a transdiagnostic, or unified approach to addressing the core psychopathology that underlies syndemic problems (i.e., psychiatric problems that co-occur frequently with HIV), may also prove to be an efficient, effective, and portable intervention strategy in the context of addressing HIV self-care behaviors.

Clinical Guidelines

The assessment of depression and depressive symptoms among individuals living with HIV can be challenging for clinicians. Given that HIV is a chronic medical illness, parceling out depressive symptoms from HIV symptoms is difficult. Because of this overlap in somatic symptoms (e.g., fatigue, concentration/memory difficulties, appetite and sleep changes) in some cases, clinicians are encouraged to weigh cognitive and emotional symptoms of depression in assessing this population. At the same time, this may be a bit of a balance, because in some cultures and for some patients, depression may present somatically. It may be useful to examine scoring of assessments both with and without the somatic items, as can be done, for example, with the Beck Depression Inventory (BDI; Beck et al., 1961, 1988).

Treating depression in HIV-infected patients within a CBT framework largely mirrors CBT for the general population; however, there are some subtle yet important differences. One area that we have found to be particularly important in our work with this population is including problem-solving strategies within sessions. As mentioned above, individuals living with HIV often grapple with numerous psychosocial stressors which, in the context of clinical depression, can make even small problems appear daunting and overwhelming. First we elicit from patients what is the most pressing problem they are currently facing; then we ask "why is this a problem for you?" Next, we encourage the patient to take the lead in compiling an exhaustive list of possible solutions. Only once this list is completed will the clinician and patient review each solution and evaluate its pros and cons. Not only do we utilize this problem-solving approach broadly but we also specifically apply problem-solving techniques to aid in patients' medication adherence. In our experience we have also noted that CBT homework adherence tends to be rather low; thus clinicians working with this population should be flexible in assigning and evaluating homework. It may be necessarily to break homework assignments down into the most basic elements and query patients whether they believe that they can complete the task. If they report that they cannot, we assess barriers and revise the homework assignment. Similarly if a patient has not completed a homework assignment, clinicians should work in session to uncover the barriers

and meet the patient where he or she is in regard to motivation to change.

Regarding psychosocial interventions, although the empirical data from RCTs are mixed, we believe that a CBT approach is a useful first-line psychosocial treatment to apply in working with depressed HIV-infected patients. We should also note that IPT has shown some success in treating depression in this population; this approach should also be considered. As for modalities, we have found through our own work that group-based interventions are difficult to implement for a number of reasons. Patients have provided feedback that if they were to participate in a group, they would prefer a group that consisted of similar members; that is, HIV-infected MSM prefer to be in groups with other MSM, while HIV-infected women prefer to be with other HIV-infected women. This clustering of groups by HIV subpopulations can prove challenging in creating and maintaining adequately sized groups, scheduling, and other logistics that are difficult to manage in a fee-for-service setting. Another important issue is that for many HIV-infected individuals, there are a number of logistical difficulties (e.g., transportation, multiple medical appointments) in scheduling and attending therapy sessions. These obstacles are compounded in attempting to accommodate multiple individuals' needs, as in the context of a group setting. Finally, our experience is that HIV-infected patients are less likely to be interested in group treatment owing to insurance issues. For example, patients are accustomed to insurance plans covering individual therapy; however, in some locations, free support groups offered by AIDS service organizations set the norm that groups are not something for which a person would need to use their insurance or a payment or copay. For these mostly logistical reasons, our program tends to favor individual treatment over group approaches.

Another salient aspect of treating depression in individuals living with HIV is relapse. Relapse is very common among depressed patients in the general population and is an even more common phenomenon among those who are chronically medically ill. Thus relapse prevention efforts must be highlighted in any approach for treating depression in this population. In our treatment (Safren, Gonzalez, & Soroudi, 2007) we specifically address relapse concerns in the final session of the intervention. In this session, we review CBT skills learned thus far and discuss the transition to "becoming your own therapist" as well as the importance of practice in maintaining gains. However, we also highlight the possibility that depression may recur and that the patient should be careful not to view relapse as a treatment "failure." We also ask patients to think about what may be some particularly challenging situations in the future and/or symptoms that they believe are likely to be problematic for them. We then map specific CBT skills to consider for each of these potentially difficult situations.

Last, we would like to call attention to the need for enhanced depression screening of all HIV-infected patients in primary care/HIV care settings. As discussed in the literature above, depression is often underdiagnosed in this population and has the potential to adversely affect not only quality of life but also medication adherence, disease progression, and consequently mortality. Given this, we encourage the routine screening of all HIV-infected patients as part of their primary care visits. This need not be a laborious undertaking for clinicians or patients. By simply administering the briefest of measures, such as the PHQ-2 (Kroenke, Spitzer & Williams, 2003), PHQ-9 (Kroenke & Spitzer, 2002), or the publicly available CESD (Radloff, 1977), clinicians can glean important information about depressive symptoms and make appropriate referrals for psychotherapy and/or psychopharmacology.

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CHAPTER

25 Depression in Chronic Kidney Disease: A Context for Comorbidity

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Abstract

Chronic kidney disease (CKD) is a prevalent medical condition posing a range of unique physical and self-management demands for patients and presenting a variety of patient management challenges for clinicians. Comorbid depression and other psychiatric disorders represent a significant detriment to the quality of life and clinical outcomes of CKD patients. Evidence suggests that 12% to 40% of individuals in the later stages of CKD meet DSM (III, IV, or IV-TR) diagnostic criteria for a mood disorder. Moreover, the existence of comorbid depression has been associated with earlier patient mortality. Depression assessment is itself complicated by the physiologic and medical treatment status of the patient, and depression is believed to be both underdiagnosed and undertreated in this population. Rigorous empirical demonstrations of the safety and/or efficacy of both pharmacologic and nonpharmacologic treatments for depression are limited for this population. However, a number of important factors that should be considered in treating depression in kidney disease patients have been identified. This chapter summarizes these and other key clinical recommendations relevant to the evaluation and treatment of comorbidity of depression in this population.

Key Words: chronic kidney disease, comorbid depression, evaluation and treatment, clinical recommendations

The prevalence of chronic kidney disease has risen steadily over the past several decades; it currently affects over 30 million people in the United States at varying levels of severity (Coresh et al., 2007; U.S. Renal Data System, 2011). For most patients the condition is secondary to another primary medical condition (most commonly diabetes mellitus or hypertension) and progresses over time from relatively mild, asymptomatic renal impairment through stages of renal insufficiency until end-stage renal disease (ESRD) is reached. The approximately 500,000 patients in the United States with advanced renal disease or ESRD face an incurable life-threatening chronic illness. ESRD is defined clinically as a total or near total cessation of kidney function such that "renal replacement intervention" in the form of renal dialysis or renal transplantation is necessary to sustain life. Disease severity and symptom burden vary greatly among ESRD patients largely as a function of the underlying etiology of their renal disease and other comorbidities. For example, patients whose renal impairment is secondary to diabetic nephropathy typically have multiple diabetic comorbidities (e.g., vascular disease, retinal disease) by the time renal failure ensues. Overall, ESRD patients in the United States have an expected five-year survival of just under 50% (U.S. Renal Data System, 2011).

A functioning renal transplant is believed to offer ESRD patients the highest quality of life and most favorable clinical prognosis (Cameron, Whiteside, Katz, & Devins, 2000; Christensen & Ehlers, 2002). Although renal transplantation requires lifelong immunosuppressant therapy and continued

medical evaluation, transplanted ESRD patients live longer, show greater mobility, are more likely to be employed, and report more favorable emotional well-being (e.g., Christensen, Turner, Smith, Holman, & Gregory, 1991; Dew et al., 1997; Port, Wolfe, Mauger, Berling, & Jiang, 1993). However, owing to a perennial shortage of donor organs, only about 30% of ESRD patients have a functioning transplant at any given time (U.S. Renal Data System, 2011). The most common mode of therapy (approximately 65% of ESRD patients in the United States), involves center hemodialysis (U.S. Renal Data System, 2011). ESRD patients on hemodialysis face a behaviorally demanding and sometimes painful or uncomfortable treatment course. A regimen of renal dialysis is also extremely time-consuming and is associated with both physiologic state and lifestyle disruptions. Center hemodialysis involves four- to five-hour treatment sessions conducted in a clinic or hospital three times weekly. During a treatment, excess fluid and toxins are rapidly removed from the body through an arteriovenous connection to a dialysis machine. While chronic hemodialysis greatly extends life, the physiologic state of uremia that ensues in the later stages of renal failure is only partially managed through the procedure and is associated with a range of physical and neurocognitive symptoms including mental status changes, extreme fatigability, anemia, nausea and vomiting, anorexia, and shortness of breath.

Assessment and Prevalence of Depression in Chronic Kidney Disease

As with many chronic medical conditions, comorbid depression and other psychiatric disorders represent a significant detriment to the quality of life and clinical outcomes of patients in the later stages of renal failure. Kimmel, Thamer, Richard, and Ray (1998) reported that hospitalization rates for psychiatric disorders are approximately twice as high among ESRD patients compared with patients with other chronic medical conditions (e.g., diabetes, cardiovascular disease, cerebrovascular disease). In this study of Medicare enrollees with chronic renal failure, the most common psychiatric comorbidities were mood disorders, dementia and substance use disorders.

Most of the attention involving depression as a psychiatric comorbidity has been focused on ESRD patients in the later stages of renal failure, with less known about patients with mild or moderate renal impairment (Kimmel, 2002). Estimates of the prevalence of depression vary substantially as a function of assessment method (Christensen & Ehlers, 2002). Depression is thought to be particularly high among ESRD patients on center hemodialysis. Evidence suggests that 12% to 40% of these individuals meet DSM (III, IV, or IV-TR) diagnostic criteria (typically assessed via clinical interview) for a mood disorder (Christensen & Ehlers, 2002; Kimmel, Cukor, Cohen, & Peterson, 2007). Among studies assessing presence of depression symptoms or syndromal depression via self-report instruments such as the Beck Depression Inventory (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), as many as 50% of ESRD patients are believed to have clinically significant levels of distress (e.g., Craven, Rodin, & Littlefield, 1988; Murtagh, Addington-Hall, & Higginson, 2007; Smith, Hong, & Robson, 1985).

A variety of factors likely contribute to the high levels of depression observed in ESRD patients, including the potential for important role losses or functional limitations posed by the renal disease or other comorbid medical disorders (e.g., loss of employment, change in family roles, changes in sexual or cognitive function). Medications (e.g., steroids, immunosuppressants, antihypertensives) used to manage the condition may contribute to depression symptoms as well (Kimmel, 2002). Moreover, among patients treated with hemodialysis, the high degree of physiologic stress associated with rapid shifts in fluid balance, electrolytes, and blood pressure, may contribute to or mimic symptoms of depression. Not surprisingly given the relative degree of intrusiveness and lifestyle disruption associated with the available treatment modalities, meta-analytic review has reported that levels of depression tend to be highest among patients managed with hemodialysis and somewhat lower for individuals with a functioning renal transplant (Cameron et al., 2000). One recent study reported that 15% of patients being evaluated for a renal transplant self-endorsed symptoms consistent with a depressive condition. The investigators interpreted these relatively low rates of depression to selection biases in ESRD patients who are potential transplant candidates and possibly to the underreporting of distress due to patients' motivation to present themselves positively during the transplant evaluation process (Kuntz & Bonfiglio, 2011).

The assessment of depression among patients with advanced kidney disease is itself challenging. This fact certainly contributes to the wide range of prevalence estimates reported previously as well as to what many believe is an underrecognition of depression in this population (Drayer et al., 2006;

Kimmel, 2002). A central issue is that neurovegetative or somatic symptoms of depression (e.g., changes in libido, sleep disturbance, fatigability) included in many syndromal and diagnostic depression measures overlap with symptoms of renal failure itself (Zalai & Novak, 2008). Many investigators have suggested that nonsomatic or cognitive or psychological symptoms of depression (e.g., dysphoric mood, guilt, anhedonia) distinguish depressed from nondepressed ESRD patients better than do somatic or vegetative criteria (e.g., Christensen & Ehlers, 2002; Craven, Rodin, & Littlefield, 1988; O'Donnell & Chung, 1997). However, there is no clear consensus regarding whether the overlapping somatic depression and uremic symptoms of ESRD should be included in the assessment and diagnosis of depression (Zalai & Novak, 2008). In addition to cognitive symptoms, researchers have also proposed that focusing on more subjective indicators such as social withdrawal or tearfulness may better capture depression in chronic illness populations (Simon & Von Korff, 2006).

Not surprisingly, diagnostic assessment can vary widely depending upon the criteria applied. O'Donnell and Chung (1997) reported that the prevalence of depressive disorders dropped from 34% to 6% when somatic indicators were excluded from diagnostic criteria. In any clinical population, diagnostic guidelines emphasize the need to distinguish signs and symptoms of depression from those directly attributable to a medical condition (e.g., American Psychiatric Association, 2000). However, the impact of renal failure is systemic. Given the psychosocial and physical challenges associated with the disease, the highly intrusive nature of the available treatment modalities, and the overall clinical complexity of many patients with renal failure, the differential diagnosis of depression in this population poses a substantial challenge to the clinician.

Impact of Depression on Clinical Outcomes and Patient Survival

Researchers are increasingly recognizing an association between depression and the development and progression of chronic physical illness (Katon & Ciechanowski, 2002). Perhaps the most compelling data regarding a depression/morbidity/mortality link comes from work involving the chronic kidney disease population. Although the data are not entirely consistent, an increasing body of evidence points to an association between depression and poorer renal disease patient outcomes, including earlier mortality (e.g., Burton, Kline, Lindsay, & Heidenheim, 1986; Fischer et al., 2011; Kellerman, Christensen, Baldwin, & Lawton, 2010; Kimmel, Peterson, Weihs, Simmens, et al., 2000; Young et al., 2010). Our own research team has reported that (nonsomatic as well as somatic) Beck Depression Inventory (BDI) scores obtained in the early stages of kidney failure significantly predict increased mortality among patients during an average 81-month follow-up period (see Figure 25.1) (Kellerman et al., 2010). Chilcot, Wellsted, Davenport, and Farrington (2011) assessed depression symptoms using the BDI shortly after incident dialysis patients began treatment. These authors reported that a total BDI score ≥ 16 (the conventional BDI cut score reflecting clinical depression, Sprinkle et al., 2002) was associated with a 2.7 times increase in the hazard for death. Hedayati et al. (2010) found that patients with chronic kidney disease who met diagnostic (DSM-IV) criteria for a current major depressive episode were at a significantly increased risk for a poor clinical outcome (e.g., hospitalization, progression to dialysis) over the ensuing year. Finally, a study by Kimmel, Peterson, Weihs, Simmens, and colleagues (2000) involving repeated assessments of depression over time suggested that changes in depression symptoms across the renal disease course may be a particularly potent predictor of mortality risk.

Given an apparent association between depression and mortality in this population, understanding the underlying mechanisms is important to comprehending the causal chain and identifying optimal targets for intervention efforts. Kimmel et al. (2007) and others (Christensen & Ehlers, 2002; Kimmel, 2002) have noted both behavioral (e.g., patient adherence, effect on interpersonal relationships) and physiologic (e.g., altered neuroendocrine/immune function, medication effects) mechanisms as potentially important mediators of an effect of depression on earlier mortality. Friend, Hatchett, Schneider, and Wadhwa (1997) reported a particularly interesting reciprocal relationship between higher depression and lower serum albumin values. Albumin is an important clinical marker of overall nutritional status and a strong, known predictor of survival in renal disease. In this study previously assessed depression preceded a subsequent decrease in albumin levels, suggesting one potential mechanism linking depression and patient outcome.

While a number of underlying mechanisms have been posited, empirical demonstration of mediating effects has proven much more elusive.

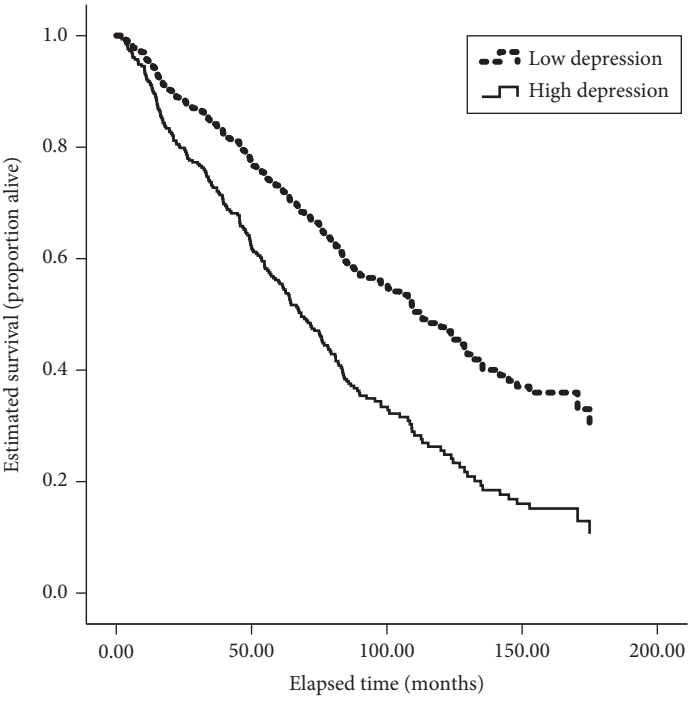

Figure 25.1 Estimated survival functions by level of total depression.
Note: High and low depression represents total depression scores one standard deviation above and below the mean, respectively, for this sample.
Source: From Kellerman et al. (2010).

For example, the association between dialysis regimen adherence and depression has received particularly strong attention in the literature, yet an association has not been clearly established (Cukor, Rosenthal, Jindal, Brown, & Kimmel, 2009; Kimmel, 2002). Indeed, very few studies have reported clear evidence that a posited mediator explains significant variance in the depression-mortality association (e.g., Kimmel, 2002). This could be because of a lack of precision in assessing the putative mediator or to the presence of unmeasured third variables. Alternatively, the mechanisms linking depression and mortality in this population may simply not yet have been accurately identified. Clearly the interrelations of depression, patient behavior, physiologic disruption, and survival are complex in this population.

Depression, Suicide, and Withdrawal from Dialysis

Notably, the suicide rate among ESRD patients has long been described as considerably higher than that in the general population and higher than in many other chronic illness populations (e.g., Abram, Moore, & Westervelt, 1971; Kimmel, Weihs, & Peterson, 1993; Kurella, Kimmel, Young, & Chertow, 2005). Very early reports among patients receiving hemodialysis reported suicide rates in excess of 100 times those seen in the general population (Abram et al., 1971). However, more recent estimates are much more moderate (Kimmel, 2002). For example, Kurella and colleagues (2005) reported an incidence of approximately twice that seen in the general population, and this estimate likely reflects the actual rate of overt suicide among patients with renal failure.

One controversial issue related to suicidal behavior in this population involves the increasing prevalence of patients forgoing lifesaving dialysis treatment (Cohen, Dobscha, Hails, Pekow, & Chochinov, 2002; McDade-Montez, Christensen, Cvengros, & Lawton, 2006). Most authors and investigators of the epidemiology of depression and suicidality do not classify death from patient-directed termination of dialysis treatment as suicide despite the fact that it results from a voluntary act of the patient (Cohen et al., 2002; Kimmel, 2002). Withdrawal from dialysis prior to death is currently the second leading cause of death among dialysis patients (behind cardiovascular disease), accounting for about 20%

of patient mortality (U.S. Renal Data System, 2011). These data are remarkable in that there is no other chronic medical condition where such a large proportion of patients without a terminal diagnosis decline to continue life-sustaining treatment. Interestingly, large cultural differences exist in dialysis termination decisions, with a much higher rate of withdrawal among Caucasian patients than among black and Asian American patients (Leggat, Bloembergen, Levine, Hulbert-Shearon, & Port, 1997).

Research involving a variety of chronic disease populations has documented an association between depressed mood and increased desire for death and other end-of-life attitudes (Breitbart et al., 2000; Ganzini et al., 1994). Not surprisingly, in the renal disease population, data suggest that depression symptoms are a significant risk factor for later treatment withdrawal decisions. Our own research team found that the estimated risk of withdrawing from dialysis for patients with BDI scores one standard deviation above the mean were 42.6% higher than for patients with average scores (see Figure 25.2) (McDade-Montez et al., 2006). This effect persisted after controlling for a variety of patient case mix factors. Patient-initiated withdrawal from a challenging but life-sustaining treatment is a complex scenario involving clinical, legal, ethical, and in some cases religious issues. However, it is our belief that if patient end-of-life attitudes and decisions are substantially influenced by a state of depression (as they seem to be in this and other populations), depression assessment and intervention should be an integral part of the clinical approach to this issue.

Risk Factors for the Development of Depression in Chronic Kidney Disease

Given the high prevalence of comorbid depression and its deleterious consequences on morbidity and mortality in patients with chronic kidney disease, considerable research has focused on understanding the factors that increase vulnerability or risk for depression. Other research has focused on variables that may serve to protect or buffer against poor adjustment to this chronic illness. Biological (e.g., inflammation), demographic (e.g., younger age, female gender), psychosocial (e.g., social support), and cognitive factors (e.g., control expectancies, illness representations) have all demonstrated associations with depressive symptomatology in chronic kidney disease (Zalai & Novak, 2008). A systematic review of the literature on psychosocial factors and depression in ESRD was recently conducted by Chan and colleagues (2011). This meta-analysis suggested that psychosocial variables—including

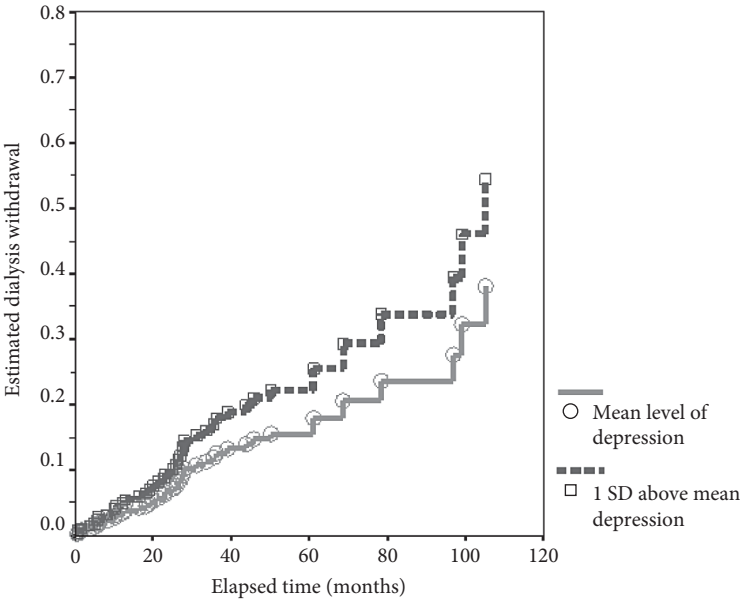

Figure 25.2 Estimated dialysis withdrawal by level of total depression.
Source: From McDade-Montez et al. (2006).

subjective and objective social support, personality attributes, cognitive appraisals, coping processes, and perceived stress—had an overall mean effect size of 0.36. The largest effects were found for personality attributes and cognitive appraisals. This pattern suggests that traits like neuroticism, an individual's tendency to endorse negative cognitions, and low self-efficacy have the strongest associations with increased depression in ESRD (Chan et al., 2011). Social support and cognitive appraisals were the most widely studied psychosocial variables in this review; thus some of the work in these areas is briefly summarized in the following sections.

Social Support

As mentioned previously, the burden and loss associated with chronic kidney disease are significant contextual factors that increase patients' vulnerability to developing depression. Researchers have suggested that perceived social support from valued individuals in patients' lives may facilitate positive psychological adjustment to the role losses suffered in chronic kidney disease (Patel, Peterson, & Kimmel, 2005; Seigal, Calsyn, & Cuddihee, 1987). In general, social support has been associated with fewer depressive symptoms in this population. Patel and colleagues (2005) reported an association between decreased depressive symptoms and greater perceived social support from family and friends as measured by the Multidimensional Scale of Perceived Social Support. Earlier work by Christensen, Turner, Slaughter, and Holman (1989) found that the degree of illness-related physical dysfunction moderated the relationship between perceived family support and level of depression in ESRD patients who had received a kidney transplant. Specifically, a less supportive family environment (as measured by degree of cohesion, expressiveness, and conflict) was related to increased depression and anxiety, but only for patients who had a high level of physical dysfunction. Family support was not related to symptoms of emotional distress in the group of patients whose functioning was less impacted by their physical condition.

As in the broader research literature on social support in chronic illness, however, evidence linking social relationships and health outcomes in chronic kidney disease has been inconsistent. This may be explained in part by inconsistencies in the way social support has been conceptualized and measured in previous work. In addition, the mechanisms through which social support may impact depression in this population require further delineation. Researchers have sought to examine the link between general and specific support and psychological adjustment in their work with chronic kidney disease patients (e.g., Guzman & Nicassio, 2003; Kimmel, Peterson, Weihs, Shidler, et al., 2000; Symister & Friend, 2003). Symister and Friend (2003) found that self-esteem served to mediate the relationship between social support and depression; specifically, general social support was associated with higher self-esteem, which was then associated with decreased depression. They also found that belonging support, a measure of feeling connected and socially integrated with others in a variety of activities, predicted fewer symptoms of depression (Symister & Friend, 2003). In addition to studying the effects that social relationships can have on favorable adjustment to ESRD, these investigators have also sought to better understand more specific aspects of the social support construct, such as illness-related family expectations and their association with depression. The authors found that the expectations of others regarding the patient's ability to cope with his or her illness, taking responsibility for managing the patient's treatment, and performing routine daily functions were often incongruent with the patients' own beliefs (Hatchett, Friend, Symister, & Wadhwa, 1997; Symister, 2011). Moreover, patients' perceptions of family and friends expecting too much of them has been related to increased depression independent of the effects of general social support and negative affect, both cross-sectionally and at three-month follow-up assessments (Hatchett et al., 1997; Symister, 2011).

In a review of the broader chronic illness literature, Rosland, Heisler, and Piette (2012) explored the effects of family member behaviors and communication patterns on psychological adjustment, disease self-management, and clinical outcomes in patients with arthritis, cardiovascular disease, diabetes, and ESRD. The one included study with ESRD patients by Kimmel, Peterson, Weihs, Shidler, and colleagues (2000) found that, for women, greater marital satisfaction and reports of positive interpersonal behaviors and better communication within the marital dyad was associated with more perceived social support and less depression. In general, level of marital satisfaction can influence perception of social support and reports of depression in patients with ESRD receiving hemodialysis treatment (Cukor, Cohen, Peterson, & Kimmel, 2007). Another important consideration is that marital dissatisfaction has been associated with increased

depressive symptoms in spouses of ESRD patients, and significant relationships between spousal and patient depression have been reported (Daneker, Kimmel, Ranich, & Peterson, 2001). These findings suggest that further exploration of the effects of partners' and family members' psychological adjustment on patients' perceptions of support and level of depression is warranted.

There is some evidence to suggest that individual difference variables, such as personality characteristics, may moderate the relationship between social support and depression (e.g., Hoth, Christensen et al., 2007). For example, in a longitudinal study involving a sample of patients with early-stage chronic kidney disease, Hoth and colleagues (2007) reported that greater social support among individuals high in trait agreeableness was associated with a decrease in depressive symptoms at 18-month follow-up. However, social support had little effect on depression change for individuals low in agreeableness. Thus, both contextual (e.g., disease severity) and patient (e.g., personality traits) considerations may moderate the effects of support on depression in this population.

Cognitive Factors

Cognitive appraisal variables such as health locus of control (Christensen & Ehlers, 2002; Cvengros, Christensen, & Lawton, 2005), illness representations (Chilcot et al., 2011), negative illness schemas (Guzman & Nicassio, 2003), and illness intrusiveness (Christensen & Ehlers, 2002; Devins, 1994; Devins, Hunsley, Mandin, Taub, & Paul, 1997) have been found to be associated with risk for depression in chronic kidney disease. Internal health locus of control (HLOC) reflects individuals' beliefs about whether they can control outcomes related to their health with their own personal behavior (as compared to health outcomes being determined by chance/luck or controlled by others, such as their physician or family members). Given the unpredictable and progressive nature of the disease course in chronic kidney disease, our research team has posited that the extent to which patients expectations about control are congruent or consistent with objective constraints or realities of the illness and treatment context may impact their psychological adjustment (e.g., Christensen et al., 1991; Cvengros, Christensen, & Lawton, 2005). In one early study, Christensen et al. (1991) found that the association between health-related control expectancies and depression differed as a function of whether patients had experienced a failed renal transplant. That is, for such patients, high internal HLOC was actually related to higher depression. Among patients on dialysis who had not received a transplant, higher internal health control was associated with lower levels of depression. This pattern suggests that a mismatch between subjective level of control and actual or objective control over health-care outcomes may be predictive of greater depression in this population.

More recently, Cvengros, Christensen, and Lawton (2005) conducted a prospective examination of the association between internal HLOC and symptoms of depression in a sample of 207 chronic kidney disease patients who did not yet require treatment for ESRD. Results indicated that while baseline control beliefs did not significantly predict depression, at 16-month follow-up increases in internal HLOC over time were associated with fewer depressive symptoms in patients whose disease had progressed to ESRD. These findings underscore the importance of examining cognitive factors such as HLOC as dynamic constructs that may shift with disease severity and impact psychological adaptation in chronic illness over time.

Individuals' interpretations of their illness and its impact on their lives can also significantly influence the development of depression in this population. After controlling for variance explained by other clinical factors, Chilcot et al. (2011) found that patients with ESRD who perceived greater consequences as a result of their health status and less personal control over their illness were more likely to endorse symptoms of depression. In general, perceptions of illness intrusiveness or the extent to which the medical condition and treatment disrupt individuals' lives and impair functioning have demonstrated significant associations with increased depression in ESRD (Christensen & Ehlers, 2002; Devins, 1994; Devins et al., 1997; Griva, Davenport, Harrison, & Newman, 2010). Moreover, previous work suggests that negative illness schemas are associated with increased depression in ESRD and that positive illness schemas mediate the relationship between social support and depression in this population (Guzman & Nicassio, 2003). Given the complex nature of these interactions, it is important for future researchers to continue designing prospective studies that examine shifts in psychosocial factors over time and account for changes in the disease course in order to better understand the development of depression in chronic kidney disease.

Depression Treatment in Chronic Kidney Disease

Despite the recognized prevalence of depression in patients with chronic kidney disease as well as the demonstrated negative impact that depression can have on treatment adherence, disease course, and quality of life, depression is largely underdiagnosed and undertreated in this patient population (Hedayati, Yalamanchili, & Finkelstein, 2012; Lopes et al., 2004). In large part, the undertreatment may be secondary to a lack of evidence-based approaches to treatment of depression in this patient population (Hedayati et al., 2012). Empirical evaluation of both pharmacologic and nonpharmacologic treatments for depression have been limited by methodologic flaws and researchers cite an urgent need for large scale, randomized controlled trials (RCTs) of various methods of treatment for depression in these patients (Cohen, Norris, Acquaviva, Peterson, & Kimmel, 2007; Rabindranath et al., 2005). Such research is necessary to identify efficacious and safe treatments to alleviate depression, as well as to investigate if reductions in depression can improve clinical kidney disease outcomes (Finkelstein, Wuerth, Troidle & Finkelstein, 2008; Hedayati & Finkelstein, 2009).

Barriers to Successful Treatment

Psychological treatment of patients with chronic kidney disease is inherently complex due to biological, psychological, and environmental factors affecting treatment decisions. To be effective, treatments should be tailored to the patient's needs and the clinic's resources (Hedayati et al., 2012). As discussed earlier, it can be difficult for patients and providers to distinguish between the somatic and affective components of depressive symptoms as well as to distinguish depression from the medical illness (Cukor & Friedman, 2005; Hedayati & Finkelstein, 2009). For example, Johnson and Dwyer (2008) reported that 50% of the hemodialysis patients with elevated BDI scores were unaware of their depression. These investigators contend that the most prominent barrier to treatment of depression is patients' lack of awareness of their condition. Alternatively, Cohen and colleagues (2007) suggest that the prominence of somatic rather than affective depressive symptoms influences providers' undertreatment of depression in patients with chronic kidney disease.

Wuerth, Finkelstein and Finkelstien (2005) found that over half (55%) of patients with elevated BDI scores refused further assessment for a clinical diagnosis of depression and subsequent treatment. These patients denied or minimized depressogenic symptoms and expressed concern regarding stigmatization or mental weakness associated with a diagnosis of depression (Wuerth et al., 2005). In an observational study, Johnson and Dwyer (2008) found that 16% of their sample reported feelings of anxiety and/or depression but felt they did not need help and could improve without intervention. Alternatively, Cukor (2007) reported that patients perceived their depression to be a necessary comorbidity that was part of their overall illness experience. Individuals' own illness perceptions must be considered in assessing and treating depressive symptoms.

When a patient with chronic kidney disease receives a diagnosis of depression, treatment initiation and completion are variable. Some patients are hesitant to engage in pharmacologic treatment, as they already have a complex condition necessitating a structured treatment and medical regimen (Cukor & Friedman, 2005; Wuerth et al., 2005). Additionally, the significant time required for dialysis often leads patients to resist the addition of another recurring appointment, such as psychotherapy, to their schedule (Cukor, 2007; Finkelstein et al, 2008).

Pharmacologic Treatment

Depending on the method of depression assessment, only 16% to 50% of patients with comorbid chronic kidney disease and depression are treated with antidepressant medication (Hedayati & Finkelstien, 2009; Lopes et al., 2004). The undertreatment of these patients is limited by the lack of data regarding the safety and efficacy of antidepressant medications in this population (Hedayati et al., 2012; Hedayati & Finkelstein, 2009). Owing to concerns about the effects of reduced renal function on drug metabolism, patients with chronic kidney disease have traditionally been excluded from large RCTs of antidepressant medications in the general population (Hedayati & Finkelstein, 2009). Although pharmacologic treatment trials have been carried out in chronic kidney disease patients, these studies are limited by methodologic issues such as small sample sizes, lack of control groups, nonrandomized study designs, and lack of DSM-validated diagnoses of clinical depression (Hedayati et al., 2012; Hedayati & Finkelstein, 2009; Raymond, Wazny, & Honcharik, 2008). A comprehensive Cochrane review of pharmacologic treatment of depression in dialysis patients identified only one

qualifying RCT involving 12 depressed dialysis patients randomized to receive an eight-week trial of fluoxetine or placebo (Blumenfield et al., 1997). This study found no significant differences in depression, although it was underpowered to detect efficacy and results trended in favor of fluoxetine. This lack of RCT empirical data precludes firm conclusions regarding the safety and efficacy of antidepressant medication use in this population and demonstrates a desperate need for research in this area (Rabindranath et al., 2005).

Because of the unique medical considerations involved, expert management of antidepressant pharmacotherapy is particularly essential in working with ESRD patients. Safety concerns exist due to the possibility of interactions with other medicine taken by chronic kidney disease patients, the effect of renal impairment on antidepressant medications' pharmokinetics, and the potential for exacerbation of preexisting uremic conditions (Cohen et al., 2007; Hedayati & Finkelstein, 2009; Rabindranath et al., 2005). The high protein-binding properties of some antidepressant medications cause them not to be removed by dialysis, leading to the potential toxicity of metabolite accumulation due to decreased renal clearance (Cohen et al., 2007; Hedayati et al., 2012; Hedayati & Finkelstein, 2009). In general, selective serotonin reuptake inhibitors (SSRIs) are considered much safer than monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants in kidney disease patients because they involve fewer side effects (particularly important for patients with comorbid cardiovascular disease) and drug interactions (Cohen et al., 2007; Raymond et al., 2008). It is generally recommended to begin medication cautiously at the lowest effective doses, with gradually increasing doses accompanied by strict monitoring for side effects and toxicity (Raymond et al., 2008; Wuerth et al., 2005). Some researchers advise reducing dosages of antidepressant medication, particularly non-SSRIs, by one third for kidney disease patients (Cohen et al., 2007; Rabindranath et al., 2005; Raymond et al., 2008). For further information on specific antidepressant medications and their suggested starting dosages, drug interactions, and adverse effects in this population, see Cohen et al. (2007), Hedayati et al. (2012), Raymond et al. (2008), and Wuerth et al. (2005).

Notwithstanding the noted methodologic limitations, statistically significant improvements in depressive symptoms have been observed for treatments of fluoxetine, sertraline, citalopram, bupropion, nefazodone, nortriptyline, and paroxetine in small samples of kidney disease patients (Kalender, Ozdemir, Yalug, & Dervisoglu, 2007; Koo et al., 2005; Levy et al., 1996; Turk et al., 2006; Wuerth et al., 2005). Despite these small scale trials indicating initial safety of antidepressant medication use in this population, recent findings suggest that safety concerns remain. Chandler, Singh, and Mukhiya (2011) found that 25 mg of sertraline, an SSRI and dose that has been considered safe in previous work, caused symptoms of hyperserotonemia ("serotonin syndrome") in all but one hemodialysis subject, with complications ranging from restlessness, agitation and anxiety, to myoclonic jerks, hypertension, and potentially life-threatening atrial fibrillation.

Nonpharmacologic Treatment

Varied alternatives to pharmacologic treatment of depression exist for patients with chronic kidney disease. Either during or adjacent to dialysis sessions, psychoeducation, psychotherapy, music and art therapy, meditation, and relaxation training have been offered to patients (Hedayati et al., 2012; Hedayati & Finkelstein, 2009). Of these, the most research attention has focused on cognitive behavioral therapy (CBT). This therapy, which in some studies has been adapted to a group setting, typically involves cognitive restructuring of dysfunctional thoughts, behavioral activation, and skills training to better cope with the effects of the disease and treatment on daily life (Cukor, 2007; Duarte, Miyazaki, Blay, & Sesso, 2009; Hedayati & Finkelstein, 2009). Unique needs of dialysis patients that could be included in CBT include recognition of the disruption to work and home life caused by dialysis, feelings of loneliness and isolation associated with time spent on dialysis, and the juxtaposition of illness hopelessness with the prospect of transplantation (Cukor & Friedman, 2005).

Duarte and colleagues (2009) found that depressed ESRD patients who were randomized to receive 12 weekly group CBT meetings (N = 41; 1.5 hour sessions) had significant improvements in depressive symptoms, quality of life, and risk of suicide compared with depressed patients who received treatment as usual (N = 44). CBT sessions included self-monitoring, cognitive restructuring, activation, relaxation, and prevention of relapse, whereas treatment as usual consisted of weekly individual psychological consultation for emotional support and treatment guidance. After the three months of active treatment, patients received monthly maintenance sessions for six months. Importantly, treatment gains were maintained at the conclusion of

this maintenance period. Although this study was strengthened by multimethod depression assessment and cost-effective treatment delivery (group settings in dialysis centers), patients in both conditions were using antidepressant medication making the CBT effects more difficult to isolate. A smaller CBT intervention ($N = 16$), which lacked randomization to treatment and control groups, found that 15 weeks of individual "chairside" CBT during dialysis was associated with significantly improved depression up to three months after the conclusion of therapy (Cukor, 2007). Although engaging in psychological treatment while dialyzing is a promising treatment modality, logistical and staffing issues at dialysis centers must be considered. For example, social workers in dialysis centers often have limited availability and other staff, such as technicians, nurses, and dieticians, have limited psychological training (Finkelstein et al., 2008). Additionally, there are ethical concerns regarding privacy and confidentiality of chairside therapy conducted in such public settings.

Additionally, it has been suggested that treatment of related issues, such as marital and family discord, problems with social interactions or deficient social support, and anxiety symptoms, could improve depressive symptomology (Cohen et al., 2007; Hedayati et al., 2012). For example, an intervention addressing psychosocial adjustment to home peritoneal dialysis provided in-home therapy to patients and their spouses jointly (Hener, Weisenberg, & Har-Even, 1996). In a quasi-experimental design, couples received either eight weekly sessions (80 minutes each) of supportive therapy ($N = 18$ couples), CBT ($N = 18$ couples), or no intervention ($N = 24$ couples). Supportive therapy encouraged emotional expression and problem solving and was socially focused, whereas CBT covered emotional, cognitive, behavioral, and interpersonal domains in a task-oriented manner. Both active interventions delivered in this study, were effective at improving couples' psychosocial adjustment across emotional, cognitive, and interpersonal domains, while the no-treatment control group demonstrated a decline in psychosocial adjustment. Although this study suggests that multiple home-based, couples therapies can be effective, its lack of follow-up sessions or assessments precludes any understanding of lasting treatment gains.

Not surprisingly, given the link between the physiologic state of uremia and symptoms reflecting depression, altering the dialysis regimen itself has been shown to be associated with improvements in depression symptoms. Increasing the dialysis "dose" from the traditional three times weekly to six times weekly ("daily") sessions seems to be associated with decreased depression presumably due to increased renal clearance, improved blood pressure control and enhanced nutritional status (Hedayati & Finkelstien, 2009; Jaber et al., 2010). However, other work suggests that the time consuming nature of dialysis is itself a salient stressor to many patients (Christensen & Ehlers, 2002). As with many chronic conditions, a balance must be struck between the management demands placed on the patient and the goal of maximizing clinical parameters.

In sum, although successful treatment of other comorbid medical illnesses and depression can inspire intervention research in this population, distinct treatment considerations must be made for treating depression in kidney disease patients. Impaired renal functioning affects antidepressant pharmacokinetics, and the burden of dialysis treatment may be a barrier to the time and patient engagement needed for psychotherapeutic interventions. Depression appears to be both underdiagnosed and undertreated in kidney disease patients, and there is a need for further empirically rigorous depression treatment research with this population. A brief summary of clinical guidelines related to both depression assessment and treatment in this population is included in Table 25.1.

Concluding Observations

Chronic kidney disease is a highly prevalent condition posing a unique set of clinical, psychosocial, and behavioral challenges to patients managing the illness and to their health-care providers. comorbidity between chronic kidney disease and psychiatric disorder is high, particularly in the case of depression, and evidence suggests that comorbid depression is associated with poorer patient prognosis including voluntary withdrawal from dialysis and earlier mortality. While a variety of factors have been examined as potential buffers and risk factors for depression in this population, few compelling associations have been established. Depression assessment is itself complicated by the physiologic and medical treatment status of the patient and depression appears to be both underdiagnosed and undertreated in kidney disease patients. Despite these challenges, we believe the chronic kidney disease context is ripe for clinical investigators interested in the comorbidity of depression and medical disorders to make a

Table 25.1 Clinical Guidelines for Depression Assessment and Treatment in Chronic Kidney Disease

[a]Depression has been underreported by patients in this population as well as underdiagnosed owing to overlap between kidney disease treatment sequelae (e.g., uremia, shifts in fluid balance) and depressive symptoms (e.g., fatigue, changes in mental status). Clinicians should assess for depression with a face-to-face interview in an environment that encourages disclosure of distress. Clinicians should focus on cognitive symptoms (e.g., dysphoria, hopelessness, anhedonia) and subjective indicators (e.g., social withdrawal) of depression.
[b]Assessment of depression in patients with chronic kidney disease should be an iterative process. Patients' experiences differ across various stages of renal failure and treatment contexts (e.g., center- versus home-based dialysis versus transplantation).
[c]Clinicians should proactively monitor regimen adherence and assess suicide risk among depressed patients. These patients are at risk for poor clinical outcomes and increased mortality as well as suicide and voluntary withdrawal from life-sustaining dialysis treatment.
[d]Clinicians should ensure that psychological interventions for patients with comorbid depression and chronic kidney disease are practical and efficient, due to the behaviorally and temporally demanding medical regimen.
[e]Given the systemic impact of chronic kidney disease, depression is best managed by clinicians working in a collaborative, multidisciplinary team approach.
[f]In treating depression pharmacologically, clinicians are advised to prescribe selective serotonin reuptake inhibitors at low starting doses, gradually increasing doses while frequently and carefully monitoring for side effects of toxicity. Research on antidepressant medication use in this population remains suboptimal, and the effects of reduced renal function on drug metabolism and interactions with other medications warrant additional monitoring.

substantial impact on the management of this growing patient population.

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CHAPTER

26 Depression in Dementia Syndromes

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Abstract

Depressive symptoms are common in many dementia syndromes, and depressive disorders are much more common in older adults with dementia than in cognitively intact older adults. Depression may be a risk factor for, or a prodromal feature of, subsequent dementia. Several neuropathological mechanisms have been suggested to explain these relationships, including the role of underlying cerebrovascular risk factors for depression and cognitive impairment. Depression also may be present in dementia as an emotional reaction to cognitive decline, or as a recurrence of early and midlife depression. Differential diagnosis between depression and dementia is essential, but complicated by problems in assessment, overlapping symptoms between the two conditions, and other medical comorbidities. Pharmacological treatment of depression in dementia may also be complicated by medical comorbidity and can run the risk for adverse reactions or interactions between medications. Psychotherapy and psychosocial interventions, however, hold some promise for effective reduction of depressive symptoms.

Key Words: dementia, depression, differential diagnosis, assessment, pharmacological treatment, psychosocial interventions

Introduction

Dementia is a term referring to a group of syndromes with heterogeneous etiologies involving a progressive decline in memory and/or other cognitive capabilities. These syndromes are characterized by acquired and persistent impairments in multiple domains of cognitive functioning (Bonelli & Cummings, 2008). According to the guidelines outlined by the American Psychiatric Association (APA) in the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision* (DSM-IV-TR; APA, 2000), the diagnostic criteria for dementia are: (a) memory impairment, (b) cognitive disturbances in at least one other domain of functioning (e.g., aphasia, apraxia, agnosia, deficits in executive functions), and (c) the deficits are severe enough to interfere with social or occupational functioning. The World Health Organization (WHO) outlines similar diagnostic criteria in the International Classification of Diseases, 10th Revision (ICD-10; WHO, 1992) and, in addition, requires that the dysfunction be present for at least six months.

When the DSM-IV-TR and ICD-10 diagnostic guidelines were created, Alzheimer's disease was used as the prototype for dementia. Therefore, memory dysfunction is a required criterion for a diagnosis of dementia. Memory impairment, however, may not be the predominant feature in all dementia syndromes (e.g., HIV-related cognitive decline, frontotemporal degeneration; Cummings & Benson, 1992; Royall, 2003). This issue is acknowledged in the proposed diagnostic criteria for the fifth edition of the *DSM* (DSM-5), which no longer requires memory impairment to be present. Rather the revised criteria require a significant cognitive decline from a previous level of functioning in *any* one or

more cognitive domains (e.g., executive/attention, memory, language, visuospatial functioning). The revisions also propose that the term *dementia* be replaced by Major Neurocognitive Disorder. They also define criteria for a diagnosis of Minor Neurocognitive Disorder when deficits represent a clear decline in one or more domains of cognitive functioning, but are not sufficient to cause a disruption in the ability to function independently.

Affecting an estimated 35.6 million people worldwide (Barkhof, Fox, Bastos-Leite, & Scheltens, 2011) and 5.4 million older Americans (Okie, 2011), dementia is caused by over 50 identified disorders (Katzman, 1986), with the most common subtypes being Alzheimer's disease, vascular dementia, dementia with Lewy bodies, and frontal lobe dementia (Henderson & Jorm, 2002). In a nationally representative population-based study of dementia in the United States (Aging, Demographics, and Memory Study; ADAMS), the overall prevalence of dementia in individuals aged 71 and older was 13.9% (Plassman et al., 2007). Across epidemiological studies, the biggest risk factor for dementia is age, with risk of developing dementia doubling every 5.1 years after age 65 (Jorm, Korten, & Henderson, 1987). For example, in the ADAMS study, dementia prevalence was 5.0% among those between ages 71–79 years old, but jumped to 37.4% among those 90 years of age or older (Plassman et al., 2007). Similarly, in the Canadian Study of Health and Aging (CSHA), prevalence of dementia in adults 65 and older was 8.0%, ranging from 2.4% among those 65–74 years of age to 34.5% among those 85 and older (Canadian Study of Health and Aging Working Group, 1994). With the aging of the baby-boomer population, individuals aged 65 and older are expected to represent approximately 20% of the population by 2050 (Federal Interagency Forum on Aging Related Statistics; FIFARS, 2008), resulting in more cases of dementia. To date there is no effective treatment for dementia, and, therefore, the syndrome represents an ever-growing public health concern.

Depression is a common comorbid condition in older adults with dementia, and depressive symptoms are particularly common in the early stages of several dementia syndromes (Ballard & O'Brien, 2002). Though estimates vary widely, the prevalence of major depression is higher among persons with dementia compared to cognitively intact older adults in general. Across studies, the mean prevalence of depressed mood among cognitively intact older adults is 15% (Blazer, 2003; Unützer et al., 1997) and the mean prevalence of individuals meeting diagnostic criteria for a depressive disorder (e.g., major depressive disorder, dysthymia) is 1% (Hasin, Goodwin, Stinson, & Grant, 2005). In comparison, the mean prevalence of depressed mood among people with dementia is 41%, and the mean prevalence of individuals meeting diagnostic criteria for a depressive disorder is 19% (Wragg & Jeste, 1989). Thus, depression is a treatable aspect for many individuals with a dementia syndrome.

In this chapter, I examine the key research and issues surrounding depression in dementia, with a focus on older adults. First, I review depression in several of the more common dementia syndromes. Then I discuss some of the complexities involved in the assessment of depression in dementia and differential diagnosis between these two conditions. In the next section, I review some of the theories behind the relationship between depression and dementia, and then some of the current theories regarding the neurophysiological correlates of this relationship. Finally, I review current data on treatment considerations for depression in individuals with dementia and conclude with some provisional clinical guidelines.

Depression in Different Dementia Syndromes

Alzheimer's disease

Alzheimer's disease is the most common type of dementia, and is estimated to account for 60–80% of dementia cases in the United States and the fifth-leading cause of death for Americans aged 65 or older (Alzheimer's Association, 2011; Kochanek, Xu, Murphy, Minino, & Kung, 2011). The prevalence rate for Alzheimer's disease doubles every 4.5 years of age after age 60 (Jorm et al., 1987). It is an irreversible and neurodegenerative disease, characterized by an insidious onset, gradual decline, and early prominent memory loss. A definitive diagnosis of Alzheimer's disease requires postmortem histopathological confirmation (McKhann et al., 1984). Thus, when an Alzheimer's diagnosis is made clinically, the diagnosis is referred to as either probable Alzheimer's disease or possible Alzheimer's disease.

Prevalence estimates for comorbid depression and Alzheimer's disease vary widely across studies due to differences in how depression was assessed and defined. Depression in Alzheimer's disease patients is typically less severe with respect to the number of symptoms, and minor depression is more common than major depression (Olin, Katz, Meyers, Schneider, & Lebowitz, 2002). Most studies find that approximately 30–50% of Alzheimer's disease

patients experience symptoms of depression, including a depressed mood (Wragg & Jeste, 1989; Zubenko et al., 2003), and 10–20% meet clinical criteria for a depression diagnosis (Wragg & Jeste, 1989). Most experience a mild to moderate level of depression symptoms, with more severe levels of depression in the less cognitively impaired individuals (Lazarus, Newton, Cohler, Lesser, & Schweon, 1987; Patterson et al., 1990; Reifler et al., 1989). In fact, one study showed that major depression is more common in mild (11.5%) and moderate (10%) Alzheimer's disease, but relatively less common in severe Alzheimer's disease (4.5%) (Lopez et al., 2003).

As is the case in most, if not all syndromes of dementia, the main limitation to the validity of a depression diagnosis in Alzheimer's disease is the overlap between symptoms of depression and symptoms of cognitive decline. Recognizing that *DSM-IV-TR* criteria for major depression may not be useful for diagnosing depression in Alzheimer's disease, the National Institute of Mental Health (NIMH) convened an expert panel to develop standardized diagnostic criteria for depression in Alzheimer's disease (Olin et al., 2002). The main modifications that were made to the *DSM-IV-TR* depression criteria for people with AD included: (a) reducing the requirement for five symptoms of depression to three symptoms; (b) removing "loss of interest" from the gateway criterion "loss of interest or pleasure"; (c) adding irritability and social isolation/withdrawal to the list of possible symptoms; and (d) omission of the requirement for the symptoms to be present "nearly every day." A recent study assessing the validity of the NIMH criteria found that baseline frequency of the depression in Alzheimer's disease patients was higher when using these criteria than when using other measures of assessing depression in Alzheimer's disease, but showed high sensitivity (94%) using *DSM-IV-TR* depression criteria as the reference (Teng et al., 2008). With regard to the *DSM-5,* it is yet to be determined whether depression in Alzheimer's disease will be coded via a fifth digit (e.g., 293.83 Mood Disorder Due to Alzheimer's Disease, With Depression Features) or as provisional criteria in the Appendix (APA, 2011).

Vascular dementia

Vascular dementia, previously termed multi-infarct dementia, is caused by vascular lesions to the brain from ischemic changes secondary to cerebrovascular disease or stroke. The second most common form of dementia, vascular dementia has been estimated to account for 10–20% of all cases of dementia in North America (Eastwood & O'Brien, 2004). Of controversy, however, is how often vascular dementia occurs in a "pure form," as 20–40% of Alzheimer's patients also present with vascular pathology (Jellinger, 2002). In addition, based on postmortem brain autopsy studies, 8–20% of all cases of dementia have been found to have mixed vascular and Alzheimer's disease pathology (Jellinger, 2002). As with Alzheimer's disease, age is the biggest risk factor for vascular dementia, with prevalence doubling every 5.3 years after age 65 (Ganguli, 2011).

Although cognitive impairment is the primary feature of vascular dementia, there are also important neuropsychiatric features associated with vascular dementia. One of the most common neuropsychiatric symptoms of vascular dementia is depression, which may be even more prevalent (Ballard, Bannister, Solis, Oyebode, & Wilcock, 1996; Lyketsos et al., 2000; Newman, 1999) and more severe (Simpson, Allen, Tomenson, & Burns, 1999; Sultzer, Levin, Mahler, High, & Cummings, 1993) in vascular dementia than in Alzheimer's disease. In fact, depression has been estimated to be present in up to 66% of all vascular dementia cases, with a mean of 32% of cases (Aarsland & Ballard, 2004). A recent study with the largest sample to date of vascular dementia patients found that 22% met diagnostic criteria for depressive disorder, not otherwise specified and an additional 14% met diagnostic criteria for major depressive disorder (Castilla-Puentes & Habeych, 2010). The prevalence for both depressive disorders were significantly greater in patients with vascular dementia compared to Alzheimer's disease patients (12% and 5%, respectively) and patients with unspecified dementia (17% and 7.5%, respectively).

One of the reasons hypothesized for higher rates of depression among individuals with vascular dementia compared to Alzheimer's disease is the differential distribution of pathology between these two diseases (Barber, 2004). Alzheimer's disease is a cortical dementia with damage initially seen in the temporal lobe and later in other cortical structures, whereas vascular dementia has a more frontal-subcortical involvement. Vascular dementia and other frontal-subcortical dementias (e.g., Huntington's chorea, Parkinson's disease-related dementia, progressive supranuclear palsy, HIV-related dementia) are associated with higher rates of comorbid depression. In fact, the prevalence of major depressive disorder in vascular

dementia is more than twice the prevalence of major depressive disorder among people without vascular dementia. Part of the reason for this high rate of comorbidity is due to the hallmark feature of this syndrome—widespread damage to the white matter. As discussed later in this chapter, this is thought to be due to the disruption of subcortical structures and networks in the brain that are involved in emotion and emotional regulation.

Dementia with Lewy Bodies

Dementia with Lewy bodies (DLB) is caused by an accumulation of Lewy bodies, or abnormal clusters of proteins, inside of cortical and subcortical neurons in the brain. Accounting for 10–25% of dementia cases (McKeith et al., 1996), DLB is often seen with concomitant Alzheimer's or Parkinson's disease. Clinically, patients with DLB exhibit more visual-spatial and executive functioning deficits early on than patients with Alzheimer's disease. Other hallmark features of DLB include visual hallucinations and fluctuations in both alertness and severity of cognitive symptoms. Depressive symptoms are also common among individuals with DLB. A study by Aarsland, Ballard, Larsen, and McKeith (2001) found that 19% of DLB patients met diagnostic criteria for major depression. The frequency of depressive symptoms in individuals with DLB ranges from 34–62% (Aarsland et al., 2001; Borroni, Agosti, & Padovani, 2008; Farina et al., 2009; Klatka, Louis, & Schiffer, 1996).

Frontotemporal Dementia

Frontotemporal dementia (FTD) is a group of related conditions that result from the progressive degeneration of the frontal and temporal regions of the brain leading to deficits in executive functioning, language, and behavioral control, as well as changes in self-awareness and personal conduct. There are three clinical subtypes of the disorder: (1) behavioral variant FTD (bvFTD), previously called Pick's disease or frontal variant FTD, (2) semantic dementia, also known as temporal variant FTD, and (3) progressive nonfluent aphasia. Early in the course of FTD, emotional blunting, social withdrawal, and apathy are common symptoms, which sometimes may be mistaken as signs of a depressive disorder. However, the prevalence of depressed mood symptoms among patients with FTD is lower than in other dementia syndromes, with only about 7–16% of FTD patients reporting any symptoms of a depressed mood (Bozeat, Gregory, Ralph Lambon, & Hodges, 2000; Mourik et al., 2004).

Frontal-Subcortical Dementias

Frontal-subcortical dementia, previously called subcortical dementia, is a group of disorders that share a primary pathology in subcortical structures (and their connections with the frontal lobe) and are characterized by memory problems (especially with spontaneous recall), slowed information processing, deterioration of complex intellectual functioning, and mood or personality changes (Bonelli & Cummings, 2008). The most common frontal-subcortical dementia syndromes include Parkinson's disease dementia, Huntington's chorea, progressive supranuclear palsy, thalamic degeneration, multiple sclerosis, and the AIDS dementia complex. (For a complete listing of frontal-subcortical dementia syndromes see Bonelli and Cummings, 2008). Vascular dementia affecting subcortical structures can also be considered a frontal-subcortical dementia, but was described earlier, and thus not included in the present discussion.

Across all frontal-subcortical dementia syndromes, depression is common, and depressive mood symptoms are more prevalent in these syndromes than in Alzheimer's disease and other cortical dementias (Lind, Edman, Karlsson, Sjogren, & Wallin, 2002; Lopez et al., 1995). Lopez et al. (1995) found that 20% of frontal-subcortical dementia patients met criteria for major depression and 60% reported a depressed mood. Studies ascertaining depression in Huntington's chorea have found a 30–40% prevalence of major depression and a 35–60% prevalence of depressed mood (Craufurd, Thompson, & Snowden, 2001; Paulsen, Ready, Hamilton, Mega, & Cummings, 2001). A systematic review of depression in Parkinson's disease patients found a 19% prevalence of major depression and a 35% prevalence of clinically significant depressive symptoms (Reijnders, Ehrt, Weber, Aarsland, & Leentjens, 2008). As is discussed later in this chapter, the link between depressive symptoms and frontal-subcortical dementia syndromes may suggest a neuropathological mechanism for the development of depressive symptoms in dementia.

Differential Diagnosis

Measurement Issues

Although depression and dementia are not mutually exclusive, differentiating these two conditions is crucial to patient care. As seen in the previous section, the prevalence estimates of comorbid depression in older adults with dementia vary tremendously. This is due to a number of issues related to the accurate assessment of depression in

the context of dementia. For one, many measures of depression rely on self-report. The memory loss and other declines in cognition that characterize dementia make such reporting extremely unreliable. In addition, existing measures of depression in dementia do not clarify the etiology of certain symptoms. For example, if an individual reports having dropped many of his or her activities and interests, this could either be due to the anhedonia features of depression or due to the cognitive deterioration of dementia.

One way to circumvent the problems inherent in using a self-report scale to assess depression in dementia is to use information provided by a caregiver. The use of caregiver proxy report alone, however, may lead to an over-reporting of depression. The Cornell Scale for Depression in Dementia (Alexopoulos, Abrams, Young, & Shamoian, 1988) is the only depression scale validated for people with dementia. It uses both caregiver and patient report of depressive symptoms, and in cases where there is a discrepancy between the caregiver and patient reports, it allows for the clinician rater to use his or her own judgment to score an item.

Overlapping Symptoms

For health care professionals who work with older adults, a common differential diagnosis problem arises when an older individual reports both depressive symptoms and cognitive complaints (e.g., problems with memory or concentration). Though the term "pseudodementia" is no longer used, it is nevertheless true that depressed older adults often report problems with memory and concentration. The nature of the memory problems in depression have been suggested to differ from the amnestic-type memory problems that are predominate in Alzheimer's disease; thus, neuropsychological testing may be particularly helpful in differentiating the memory problems and other cognitive deficits that are typical in an early neurodegenerative process from those associated with depression. Research into the neurocognitive deficits related to depression has consistently found that depressed older adults perform worse on measures of speed of information processing (Sheline et al., 2006) and some aspects of executive functioning (i.e., performance monitoring; Beats, Sahakian, & Levy, 1996). With respect to memory, data suggest that depressed individuals learn and remember less, especially under conditions that demand effortful processing (Boone et al., 1995). However, they show the same amount of memory storage and same rate of forgetting as their nondepressed, cognitively intact counterparts. In contrast, individuals in the early stages of Alzheimer's disease show an abnormally rapid rate of forgetting regardless of their initial learning ability. Finally, there has been some suggestion that deficits in executive functioning are more severe when depression occurs for the first time late in life (Palmer et al., 1996).

Medical Comorbidity

Using traditional diagnostic criteria, assessment of depression in older adults (both with and without dementia) can be complicated by comorbid age-related physical conditions, which may have symptoms common to both the physical condition and depression. Physical illnesses that can complicate differential diagnosis include cardiovascular disease, cancer, chronic pain, physical disability, and vitamin deficiency. Among adults over age 65, the prevalence of many chronic diseases is higher than in any other age demographic (Caine, Lyness, King, & Connors, 1994). Arthritis and hypertension each affect nearly one-third of adults over age 65 (National Center for Health Statistics, 2009), and cardiovascular drugs (e.g., antihypertensives, cholesterol-lowering medications) for older adults account for nearly one-fifth of all drugs prescribed in the United States (Blazer, Hybel, Simensick, & Harbin, 2000). Depression is especially prevalent among individuals with heart disease and with chronic pain from arthritis (Carney & Freedland, 2003). Finally, the incidence of hypothyroidism increases dramatically with advancing age, and often presents with clinical symptoms such as depressed mood and fatigue (Canaris, Manowitz, Mayor, & Ridgway, 2000).

Relationship between Dementia and Depression

Although dementia and a history of depression frequently coexist (Jorm, 2001), the mechanism behind this association remains controversial. Olin et al. (2002) proposed four subtypes of depression in dementia: (1) emotional reaction to cognitive decline; (2) recurrence of early and midlife major and minor depression; (3) vascular diseases associated with aging and dementia, causing depression (i.e., vascular depression); and (4) neurodegenerative process of dementia causing prodromal depressive symptoms. In addition, a meta-analysis by Jorm (2001) suggested that a history of depression nearly doubles the risk of dementia, as found by both case-control studies (RR = 2.01, 1.16–3.50)

and prospective studies (RR = 1.87, 1.09–3.20). He proposed that recurrent depressive episodes (e.g., lifelong history of major depressive disorder) trigger a glucocorticoid cascade in the brain, which, over time, causes brain damage leading to dementia. Finally, depression may exacerbate preexisting cognitive impairment, thereby lowering the threshold for the clinical manifestation of dementia (Jorm, 2001).

Although Jorm concluded that recurrent depression was a risk factor for dementia, many studies have found that depression frequently has developed for the first time close to dementia onset (Brommelhoff et al., 2009; Chen, Ganguli, Mulasnt, & DeKosky, 1999; Wetherell, Gatz, Johansson, & Pedersen, 1999; Yaffe et al., 1999). In these studies, the authors concluded that depression is a prodromal feature of dementia, suggesting that depression manifests itself as an early symptom of dementia. In fact, Brommelhoff et al. (2009) found that two-thirds of the individuals with dementia had their first episode of depression sometime during the 10 years preceding dementia onset. Further, these individuals had no history of depression prior to the preceding 10 years. They also found that a life-long history of depressive episodes, as is seen in major depressive disorder, was not associated with any increased risk of dementia. Therefore, at least some of the cases of comorbid depression in dementia may represent a continuation of the prodromal features of the dementing illness.

Not all comorbid depression can be accounted for by the risk factor or prodromal hypotheses. A study by Bassuk, Berkman, and Wypij (1998) found that depression did not precede cognitive impairment, but instead was present in the participants who had already experienced a reduction in cognitive abilities. They concluded that depression was likely to be a reaction to an individual's insight about decline in cognitive functioning, which may precede an actual diagnosis of dementia by several years. In contrast, a study by Carpenter et al. (2008) measured depressive symptoms both before and after individuals were diagnosed with dementia and found that there was no increase in depressive symptoms postdiagnosis. They concluded, that in their study population, depression was not a reaction to the actual manifestation or diagnosis of dementia.

Research into the phenomenology of late-onset depression (LOD; first episode of depression late in life) and early-onset depression (EOD; first episode of depression prior to late life) has suggested that although depressed mood is the core symptom for both, the etiology and symptom profile of these disorders are different (Brodaty et al., 2001; Gallagher et al., 2010). LOD tends to be more chronic and recurrent than EOD and the symptoms in LOD typically involve a number of somatic complaints, including sleep problems, fatigue, and a reduced appetite. In a review of research on depression in Alzheimer's disease and other dementias, Boland (2000) concluded that the comorbid depression found in dementia more closely resembles the phenomenology of LOD rather than EOD. He further suggested that late-life depression arises from anatomical damage to the brain caused by the neuropathological course of dementia. In other words, the depression is caused by the pathology in the brain that leads to cognitive impairment and eventually dementia. This could partially explain the differing rates of depression across dementia syndromes, which differentially affect varying regions of the brain.

Neurophysiology of Late-Life Depression

It has been hypothesized that patients with dementia and depression have different histopathological and neurochemical characteristics than depressed, cognitively intact patients (Liao et al., 2003). At present, the findings of available research literature do not conclusively support any specific pathogenesis. However, studies examining the neuroanatomical features of depression and dementia suggest that several types of neuropathology may contribute to the association between these two syndromes.

Cortical Atrophy

Both dementia and depression are associated with cortical atrophy. Atrophy of structures in the temporal lobe, especially the hippocampus, is also often found in patients with Alzheimer's disease (Schweitzer, Tuckwell, Ames, & O'Brien, 2001), and in an article summarizing findings of structural changes in the brain in individuals with depression, Kanner (2004) reported that decreases in hippocampal volume are directly associated with chronicity, severity, and duration of depression. In fact, as pointed out by Jorm (2001), the hippocampus is particularly suscesptible to damage from the glucocorticoid cascade, which is a proposed mechanism for how recurrent depression could lead to damage to the brain that is sufficient enough to cause dementia.

Although many neuroimaging studies have found that whole brain atrophy and ventricular dilation are

among some of the structural changes that accompany dementia, these changes also have been seen in several studies of depression (Schweitzer, Tuckwell, O'Brien, & Ames, 2002). Alexopoulos, Young, and Shindledecker (1992) compared individuals with late-onset depression (onset after age 60) and individuals with early-onset depression using CT. They found that not only did the individuals with late-onset depression have overall larger ventricles than individuals with early-onset depression, but their ventricle size was comparable to the ventricle size of individuals with Alzheimer's disease. Some of the most recent research into the neuropathology of depression and dementia, however, has indicated that LOD shows a stronger neuroanatomical correlation with white matter changes rather than with cortical atrophy (Kohler et al., 2010; Mueller et al., 2010; Starkstein et al., 2009). In fact, a study by Mueller et al. (2010) concluded that depressed mood and cognitive impairment have different pathological correlates, specifically that depressed mood is associated with microvascular ischemic white matter changes, whereas cognitive function is associated with gray matter atrophy.

White Matter Changes

Dementia, especially vascular dementia, and late-onset depression are also both associated with white matter changes (Lesser et al., 1996). The question of whether the white matter changes associated with depression are the same as those associated with dementia is somewhat more controversial. Studies have suggested an association between an increased number of white matter lesions and depression both with (O'Brien et al., 1996; Thomas & O'Brien, 2008) and without cognitive impairment or dementia (Thomas et al., 2002; Firbank et al., 2005; Jorm et al., 2005; Krishnan et al., 2006). One study found that a greater amount of total brain white-matter changes was more prevalent only in participants with late-onset depression (over age 50) compared with the early-onset and nondepressed groups (Lesser et al., 1996). Other studies have suggested that white-matter lesions are often evident among older individuals lacking any form of pathology, with the estimated prevalence varying considerably, though increasing with age (see Coffey et al., 1993).

In the context of late-onset depression specifically, Schweitzer, Tuckwell, O'Brien, and Ames (2002) concluded that the white matter changes that are common in individuals with late-onset depression were associated with cognitive impairment and that these changes were indicative of a prodrome to dementia, most likely of the vascular type. A prospective study by Heiden et al. (2005) investigated the associations between the extent of white matter brain changes and clinical outcomes in older adult depressed patients. They found that a greater number of white matter lesions were associated with a poorer outcome both cognitively and with respect to the course of the depressive illness. Thus, it is possible that the brain changes that accompany late-onset depression may have effects beyond their contribution in the development of a depressive disorder. In fact, in a recent review, Thomas and O'Brien (2008) concluded that there is ample evidence that the neurocognitive impairment seen in individuals with late-onset depression persists even after the depression has remitted.

A greater amount of cerebral-white matter change is also thought to be indicative of more severe depression with a greater number of depressive symptoms. For example, among cognitively intact older adults, both Jorm et al. (2005) and Heiden et al. (2005) found a direct association between the total number of cerebral white matter lesions and severity of depression and number of depressive symptoms. Additionally, in a population of older adults with and without cognitive impairment or dementia, Lavretsky et al. (2008) found an association between higher white matter lacunar volume and symptoms of depressed mood, anhedonia, anergia, and apathy at the time of assessment, even after controlling for cognitive status. The direction of causation from these studies was not established due to their cross-sectional study designs. One longitudinal study, however, found that white matter changes predated and independently predicted depressive symptoms in older adult participants (Teodorczuk et al., 2007), providing some evidence that white matter changes are an antecedant to depression.

Other studies have suggested that the development of late-life depression and comorbid cognitive dysfunction is dependent on the location of white matter changes. In particular, studies have shown that it is specifically white-matter lesions in the frontal lobe that are associated with a higher rate of depressive symptoms among those without dementia (Clark et al., 1998, Firbank et al., 2005). Consistent with this observation, Lesser et al. (1996) found that the late-onset group showed deficits in executive functions, which suggests frontal-lobe involvement. In addition, for nondepressed older adults, a greater degree of frontal-lobe white matter

changes is shown to be associated with more severe levels of dementia due to AD or vascular dementia (Capizzano et al., 2004).

Lesions in the subcortical white matter are also associated with late-onset depression (Schweitzer et al., 2002). Hickie et al. (1995) evaluated 39 hospital inpatients over age 60 with severe depression and found an association between later age of first depressive episode and increased subcortical deep white matter hyperintensities. After a mean follow-up time of 14 months, they found that 27% of the original 39 inpatients developed a probable dementia syndrome, which was predicted by a later age of depression onset and subcortical deep white matter lesions (Hickie, Scott, Wilhelm, & Brodaty, 1996). This result again suggests that individuals with late-onset depression may experience a worse cognitive trajectory than those with early-onset depression or no depression.

Basal Ganglia-Thalamic Lesions

Some of the earliest studies investigating structural brain abnormalities in affective disorders noted the prevalence and severity of subcortical hyperintensities among depressed older adults. For example, Coffey, Figiel, Djang, and Weiner (1990) compared subcortical lesions in both normal and depressed older adults (60 years of age and older) and found that lesions in the subcortical gray matter nuclei (basal ganglia and thalamus) were significantly more common in the group of depressed older adults than in non-depressed older adults. In addition, they also found that depressed older adults with a history of neurologic illness, such as mild dementia or stroke, had the highest prevalance of moderate to severe subcortical hyperintensities. Greenwald et al. (1998) sought to further localize the subcortical lesions specific to late-life depression, by comparing the subcortical gray matter hyperintensities in a group of older adults receiving treatment for depression to a group of older adult-community controls. They found that lesions in the putamen significantly predicted assignment into the depressed group. As the putamen is a component of the striatum, this finding also supports the fronto-striatal hypothesis of vascular depression (see later).

The association between striatal lesions and late-onset depression could explain the higher rates of depression among frontal-subcortical dementia patients. There has also been some evidence that suggests that concomitant damage to subcortical structures may be associated with depression in cortical dementias such as Alzheimer's disease. For example, in a recent study, Brommelhoff, Spann, Go, Mack, & Gatz (2011) found that among individuals with Alzheimer's disease, there was a significant relationship between late-onset depression and a greater amount of damage in the striatum, but no relationship between late-onset depression and white matter lesions.

Cerebrovasular Disease

There is increasing evidence that the pathogenesis of white matter lesions is largely due to cerebrovascular disease (CVD; Jagust et al., 2008). One study (Jefferson et al., 2007) indicated that cardiac insufficiency, one of the sequelae of cardiovascular disease, results in a hypoperfusion (decreased blood flow) of blood in subcortical regions of the brain. Fronto-subcortical loops and the associated white matter tracts seem to be especially vulnerable to hypoperfusion and ischemia (Chui, 2007). Thus, it would follow that even in the absence of a stroke, brain damage seen as white matter changes could occur secondary to the systemic hypoperfusion and ischemia caused by CVD risk factors. In her review focusing on subcortical ischemic vascular dementia, Chui (2007) posits that deep white matter lesions can disrupt frontal-subcortical loops and the white matter tracts therein, which are important for both cognition and emotion. Indeed, depression is common in heart disease (Carney & Freedland, 2003), and in conjunction with the vascular-depression hypothesis discussed in the next subsection (Alexopoulos et al., 1997), it would stand to reason that CVD be considered as a potentially important mechanism in the relationship between late-onset/late-life depression and dementia.

Vascular Depression

There is an ever-growing body of literature that suggests that a subset of late-life depression, particularly late-onset depression, is unique in that it is the result of age-associated cerebrovascular lesions. The vascular depression hypothesis (Alexopoulos et al., 1997) states that the sequelae of cerebrovascular disease, such as cerebral-white-matter lesions, may cause or exacerbate late-life depression. In addition, location of these lesions may be important. As an extension of this hypothesis, the fronto-striatal hypothesis of vascular depression (Shah, Glabus, Goodwin, & Ebmeier, 2002) suggests that damage specifically to the frontal lobe and striatum (input nuclei for the basal ganglia comprised of the caudate nucleus and the putamen), and/or lesions within

the frontal-subcortical circuitry, are responsible for late-onset depression.

Since its inception, there has been some disagreement about how to define the diagnostic features of vascular depression. Many studies have shown that late-onset depression seems to be particularly resistant to antidepressant treatment (Sneed & Culang-Reinlieb, 2011) and is often paired with deficits in executive functioning. Alexopoulos, Kiosses, Klimstra, Kalayam, and Bruce (2002) proposed the depression executive dysfunction (DED) disorder that defines the diagnostic criteria as late-onset depression (age 65 or older) in the presence of vascular disease and executive dysfunction. Krishnan et al. (2004), on the other hand, proposed a subcortical ischemic depression (SID) that defines the diagnostic criteria in terms of late-onset depression in the presence of MRI evidence of cerebrovascular-white matter pathology. Given the similar neuropathologies of vascular depression and vascular dementia and other frontal-subcortical dementias, there has been some conjecture that the cognitive impairment seen in vascular depression is the same entity as vascular dementia (Thomas, Kalaria, & O'Brien, 2004).

Treatment Considerations

Historically, older adults have been underrepresented in randomized-control treatment studies of depression, and in particular, in randomized-control trials of antidepressant medication. In recent years, treatment of depression in older adults has received slightly more attention; however, the individuals typically included in these studies are relatively healthy, cognitively intact, and "young" old, community-dwelling (i.e., noninstitutionalized) outpatients. Therefore, the applicability of these data to individuals with concurrent comorbidities, including dementia, is questionable.

Pharmacological Interventions

Randomized controlled double-blinded clinical trial studies of antidepressant medication for the treatment of comorbid depression and dementia are scarce. Early trials of antidepressant treatment indicated no difference between medication and placebo-control groups (Passeri et al., 1993; Reifler et al., 1989), and the anticholinergic effects of tricyclic antidepresants, in particular imipramine, was found to further impair cognition among patients with dementia (Reifler et al., 1989). In a recent systematic review and meta-analysis of placebo-controlled antidepressant studies in people with comorbid depression and dementia (Nelson & Devanand, 2011), only seven trials between 1989 and 2010 met selection criteria. Of these seven studies, five showed no significant difference between the treatment and placebo groups with respect to reduction of depressive symptoms. Only two trials, one using clomipramine (Petracca, Teson, Chemerinski, Leiguarda, & Starkstein, 1996) and the other using sertraline (Lyketsos et al., 2003), indicated a significant reduction in depressive symptoms for the treatment (versus placebo) group. Overall, the meta-analysis found that the evidence for antidepressant treatment did not confirm efficacy. Finally, another recent randomized control trial assessed the efficacy and safety of the two most commonly prescribed antidepressants, sertraline and mirtazapine, compared with placebo in a group of older adults with depression and Alzheimer's disease. This trial found that decreases in depression scores after 13 weeks and after 39 weeks did not differ between the placebo group and either of the antidepressant groups (Banerjee et al., 2011). Furthermore, the control group had significantly fewer adverse reactions than the sertraline or mirtazapine groups. Thus, Banerjee et al. concluded that use of these antidepressants for first-line treatment of depression in Alzheimer's disease should be reconsidered due to the absence of benefit compared to placebo and increased risk of adverse events.

Psychotherapy and Psychosocial Interventions

In recent years, the empirical evidence for the efficacy of psychosocial interventions for depression in dementia has grown. A 2005 review of the literature between 1994 and 2004 identified 11 randomized controlled clinical trials of nonpharmacological treatment of depression in older adults with dementia (Teri, McKenzie, & La Fazia, 2005). Seven of these treatments indicated a significant decrease of depressive symptoms in the treatment groups compared to controls, and in six of these studies, the benefits extended beyond the active-treatment period. A common theme among these treatments was the importance of working with the patients' caregivers and teaching them treatment strategies such as facilitating pleasant social interactions and problem-solving around the unique difficulties caused by dementia.

One of the seven successful behavioral approaches to treating depression in dementia incorporated pleasant events and behavioral problem solving (e.g.,

environmental modification, distraction, communication) with dementia outpatient/caregiver dyads. The study revealed a significant reduction in depressive symptoms compared to controls for not only the patient but also the caregiver. Moreover, these improvements were still maintained after 6 months (Teri, Logsdon, Uomoto, & McCurry, 1997). Several years later, this intervention was extended to include a caregiver-supervised exercise program that included training in behavioral strategies that encouraged exercise and decreased problem behaviors associated with increased activity (Teri et al., 2003). In this study, depression was significantly decreased for participants in the active group compared to controls, and these improvements were maintained at the 24–month follow up for those with higher baseline levels of depression.

Rates of depression in dementia are even higher among nursing-home residents (Even & Weintraub, 2010), and for these patients decreasing social isolation may be particularly important in reducing depressive symptoms. In addition to the behavioral approaches, psychosocial treatments for depression in dementia include social engagement approaches, which propose that mood can be improved by giving people with dementia an increased sense of control over their environment, distracting them from negative thoughts, and decreasing social isolation. Buettner and Fitzsimmons (2002) sought to improve depressive symptoms in patients with dementia by combining behavioral activation with the social-engagement approach, using therapeutic biking, which utilized a modified bicycle that attached to a wheelchair in front, where the resident sat, and was pedaled by a care partner. After the 10–15 minute rides outside the residential facility, participants met in groups to discuss the experience. Compared to the control group, depression scores decreased significantly in the therapeutic biking residents at posttest and follow up. Similarly, depressive symptoms in nursing-home residents with AD were reduced through an intervention incorporating a comprehensive exercise program, supervised walking, and social conversation (Williams & Tappen, 2008).

Psychotherapy. The assumption that persons with cognitive impairment and dementia cannot benefit from psychotherapy is a fallacy, and there is a growing body of evidence illustrating the efficacy of brief, evidence-based psychotherapy for depressed older adults with cognitive impairment. For example, a recent randomized controlled trial examined the efficacy of problem-solving therapy (PST) versus supportive therapy (ST) in depressed older adults with executive dysfunction. Alexopoulos et al. (2011) found that after 12 weeks of treatment, the individuals in the PST group showed a significant reduction in disability and depressive symptoms compared to the ST group. Furthermore, the differences between the PST and ST group were even greater in patients with greater cognitive impairment. Interpersonal psychotherapy and cognitive behavioral therapy have also shown promise as effective interventions for late-life depression, and warrant further investigation about whether they would also be efficacious among people with cognitive impairment.

Clinical Guidelines

Over the next 10 years, as the baby boomer generation continues to age, the demographic composition of the United States will show a significant increase in the proportion of adults over age 65. At the same time, the number of older Americans with dementia is expected to rise by 1.5 million (Karel, Gatz, & Smyer, 2011). Given the high comorbidity between depression and dementia, the need for evidence-based guidelines for treating older adults with depression and cognitive dysfunction/dementia will become ever more critical. Given the current body of research, it is possible to tentatively suggest some provisional clinical guidelines, outlined in the following subsections.

Assessment and Diagnosis

As outlined previously in this chapter, issues of measurement, overlapping symptoms, and medical comorbidity complicate diagnosing depression in the context of dementia. Thus, a thorough face-to-face interview with patients is not only helpful, but also necessary. An evaluation should include screening for depressive symptoms and potential for suicidality, as well as an assessment of potential contributing medical conditions and medications, which may exacerbate depressive symptoms. In addition, proxy reports from relatives and/or caregivers should also be considered, especially for individuals with more severe levels of cognitive impairment. Finally, when issues of differential diagnosis between depression and early-stage dementia arise, a neuropsychological evaluation is appropriate.

Treatment

As outlined in the previous section, there is scant evidence for the efficacy of pharmacological

treatment for depression among individuals with dementia. In fact, studies have suggested that late-life depression may be particularly resistant to antidepressant medication among individuals with concurrent cognitive impairment (Sneed & Culang-Reinlieb, 2011). More promising are psychosocial and behavioral therapy approaches, such as behavioral activation and social engagement. In addition, involving caregivers not only appears to enhance and prolong treatment outcomes for the person with dementia, but also decreases depressive symptoms in the caregiver. Psychotherapy treatment approaches also hold potential promise. A relatively recent finding indicated that problem-solving psychotherapy was effective in reducing disability among older depressed patients with cognitive dysfunction (Alexopoulos et al., 2011). Future studies could explore the efficacy of problem-solving therapy and other evidence-based treatments of late-life depression among depressed patients with mild dementia. Finally, depression in dementia is recurrence-prone condition. Thus, future research should also investigate the merits of a continuous-care model of intervention, which would involve long-term follow-up care with booster sessions to maintain treatment efficacy over time.

Models of Care

The challenges of assessment and treatment of the depressed, older adult with cognitive impairment or dementia point to the need for a cooperative, multidisciplinary approach involving medicine, clinical psychology, neurology, neuropsychology, and other related disciplines in order to provide the most comprehensive care. The current body of literature suggests that older adults tend to underutilize specialty mental health care (Karlin, Duffy, & Gleavs, 2008) and are more likely to receive services in primary-care settings (Bartels et al., 2004). This poses a problem in that health-care workers in these settings may not have the training or resources to detect and treat depression in the cognitively impaired older adult.

Given the aging population demographics, addressing this disconnect will become an increasingly greater public health challenge. One way to address this is through education and outreach in the community. Another long-term goal would be a general shift toward integrated models of care, which would ensure better communication between the many health professionals a patient may see. An example of a health-care system that uses the integrated health care model that can be found in the Veterans Affairs Health Care System, which integrates both primary care and special mental health care across a variety of settings.

Conclusions

Depressive symptoms are common in many dementia syndromes, and depressive disorders are much more common in older adults with dementia than in cognitively intact older adults. Differential diagnosis between these two disorders is essential for patient care. Assessment of depression in the context of dementia, however, is complicated by the overlapping symptoms between the two conditions, and cognitive deficits, which may impact the validity of a patient's self-report. Although caregiver proxy report of depression symptoms is a way to circumvent this issue, this procedure may lead to an over-reporting of depression. Therefore, assessment strategies, such as the Cornell Scale for Depression in Dementia, which uses information from both the patient and caregiver and is validated for people with dementia, are recommended.

There are several hypotheses regarding the specific mechanisms linking depression and dementia, including depression as a risk factor or prodromal feature for depression, vascular diseases associated with aging and dementia, causing depression, and depression as an emotional reaction to cognitive decline. Importantly, these mechanisms are not mutually exclusive, and these numerous etiologies reflect the heterogeneous clinical presentations of both conditions. In the last few decades, the role of cardiovascular disease in the relationship between depression and dementia has received considerable attention, and has led to the concept of late-onset depression as a separate entity from early-onset depression. The vascular depression hypothesis states that cerebrovascular disease causes structural damages to white matter in the brain that disrupt the neural circuitry, specifically the frontostriatal circuitry, that is necessary for maintaining both mood and cognition.

Treatment of depression in dementia may be particularly complicated by medical comorbidity and the risk for adverse reactions or interactions between medications. Indeed, the efficacy of pharmacological treatment of depression in individuals with dementia is yet to be established. Psychosocial interventions hold some promise for effective reduction of depressive symptoms, especially those treatments that incorporate behavioral problem solving, behavioral activation (e.g., exercising), and/or social engagement, and involve both the patient and caregiver. In addition, the effectiveness

of these interventions may extend beyond the active-treatment period. Finally, there is a growing body of evidence illustrating the efficacy of brief, evidence-based psychotherapy for depressed older adults with cognitive impairment.

In older adults, depression is associated with chronic medical conditions, decreases in subjectively reported quality of life, and functional disability, (Patten, 1999; Steffens, Hays, & Krishnan, 1999), and is more common in older adults with dementia than in cognitively intact older adults. Thus, for older adults with dementia and late-life depression, there are important public health implications for creating empirically validated clinical guidelines and standards for treating these two conditions. Given that many treatments for depression are mediated by neurobiological factors, the efficacy of these treatments may be compromised in individuals with neuroanatomical abnormalities. An understanding of the unique brain changes associated with dementia versus those associated with depression may elucidate avenues for treatments with better efficacy in older adults.

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CHAPTER

27 Women's Health: Comorbidity of Depression and Type 2 Diabetes, Fibromyalgia, and Rheumatoid Arthritis

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Abstract

Major depressive disorder (MDD) is a significant mental health problem with deleterious effects, including poor health related quality of life and long-term disability. Epidemiological studies suggest that women in particular are more vulnerable to an increased risk of depression, relative to men, beginning at the time of menarche through the menopausal transition. Depression comorbid with chronic medical conditions can often exacerbate the risk of depression, as well as complicate its recognition and treatment. Depression comorbidity can lead to negative outcomes, including progression of the chronic medical condition, poor treatment adherence, and mortality. In this chapter, we explore chronic medical conditions that are associated with a greater prevalence of depression in women relative to men, including type 2 diabetes, fibromyalgia, and rheumatoid arthritis. An overview of epidemiology is followed by a discussion of theories explaining depression comorbidity and approaches to recognizing and treating depression in the context of these chronic medical conditions. Finally, we discuss future research directions with the goal of informing clinical research and practice.

Key Words: chronic pain, comorbid depression, fibromyalgia, rheumatoid arthritis, type 2 diabetes, depression in women, chronic medical conditions

Introduction

According to the World Health Organization, major depression is a leading cause of disability, decreased productivity, and increased use of health care resources (World Health Organization, 2008). The lifetime prevalence of major depressive disorder is approximately 17% in the U.S. population (Kessler, Chiu, Demler, Merikangas, & Walters, 2005). More specifically, the lifetime prevalence of depression in women is over 20%, approximately twice that of men (12%) (Kessler, 2005). The risk of depression in women is even greater in the presence of chronic medical conditions such as type 2 diabetes (Anderson, Freedland, Clouse, & Lustman, 2001), fibromyalgia, and rheumatoid arthritis (Crowson et al., 2011; Munce & Stewart, 2007). Depression in these chronic medical conditions is associated with higher levels of pain, fatigue, and poor health related quality of life (Wolfe & Michaud, 2009), with combined effects leading to increased health-care utilization, direct health-care costs (Covic et al., 2012; de Groot, Anderson, Freedland, Clouse, & Lustman, 2001), and mortality (Egede, Nietert, & Zheng, 2005; Pincus, 2007). In this chapter we review the epidemiology, pathophysiology, assessment, and treatment literature on depression comorbid with type 2 diabetes, fibromyalgia, and rheumatoid arthritis in women. In turn, clinicians will be better equipped to recognize and treat depression in the context of these medical conditions and to pursue targeted research directions that will further support the literature on depression comorbid with type 2 diabetes, fibromyalgia, and rheumatoid arthritis in women. For the purpose of

this chapter, the term *depression* refers to elevated symptoms of depression unless otherwise noted.

Type 2 Diabetes

According to the National Health and Nutrition Examination Survey, which provides pooled estimates of diagnosed and undiagnosed diabetes at the national level from 2003 to 2006, the prevalence of diabetes (type 1 and type 2) among U.S. adults under 30 years old was 13.7% for men (95% confidence interval [CI] [12.0%, 15.4%]) and 11.7% for women (95% CI [10.4%, 13.0%]; Danaei, Friedman, Oza, Murray, & Ezzati, 2009). One study in particular showed that the prevalence of depression was significantly higher in a diabetic than in a nondiabetic group, with a greater number of type 2 diabetics (19.0%, n = 958) endorsing depressive symptoms, compared to type 1 (15.2%, n = 223; Engum, Mykletun, Midthjell, Holen, & Dahl, 2005). Meta-analytic findings show that women also experience more comorbid depression in the presence of type 2 diabetes than men (odds ratio [*OR*] = 1.6, 95% CI [1.4, 1.8]; Anderson et al., 2001). Type 2 diabetic patients with comorbid depression experience a more severe form of the disease and are more likely to engage in risky health behaviors, including smoking, poor diet, and physical inactivity relative to nondepressed diabetic patients (Katon et al., 2010). As a consequence, depression comorbidity leads to adverse diabetes-related outcomes that are pervasive and manifested in poor self-management, including lack of adherence to a healthy diet, exercise regimen, and maintenance of blood glucose levels (Gonzalez, Peyrot, et al., 2008; Katon et al., 2004; Lustman et al., 2000). Further, depression is associated with increased risk of diabetes complications, (de Groot et al., 2001), decreased quality of life (Egede et al., 2005), and increased risk for mortality (Katon et al., 2005). Because type 2 diabetes is more common than type 1 diabetes in the United States and has a higher prevalence of depression comorbidity in women relative to men, the focus of this chapter is on type 2 diabetes.

A substantial body of evidence suggests that depression is associated with an increased risk of incident diabetes (e.g., Knol et al., 2006; Mezuk, Eaton, Albrecht, & Golden, 2008; Pan et al., 2010), as well as for the hypothesis that diabetes may be a risk factor for the onset of depression (Katon et al., 2004; Mezuk et al., 2008; Pan et al., 2010). In one study examining the association between baseline depressive symptoms and the risk of developing type 2 diabetes (Arroyo et al., 2004), female nurses ages 45 to 72 years were screened for diabetes. Those who did not meet criteria for diabetes were assessed for depression using the five-item Mental Health Index from the Medical Outcomes Study 36-Item Short-Form Health Status Survey (Ware & Sherbourne, 1992). At a four-year follow-up assessment, age-adjusted relative risk of developing type 2 diabetes for women with depressive symptoms at baseline (based on the five-item Mental Health Index score > 52) was 1.55, 95% CI [1.27, 1.90]. After adjusting for common risk factors associated with diabetes including smoking and physical inactivity, the relative risk of type 2 diabetes in women with depressive symptoms was 1.22, 95% CI [1.00, 1.50] (Arroyo et al., 2004). Further, Mezuk et al. (2008) conducted a meta-analytic review that detected a stronger association between baseline depression and onset of type 2 diabetes (relative risk = 1.60, 95% CI [1.37, 1.88]), in comparison with that between type 2 diabetes and incidence of depression (relative risk = 1.15, 95% CI [1.02, 1.30]).

A more recent prospective study investigated new onset cases of type 2 diabetes in a population of women ages 50 to 75 years (Pan et al., 2010). Relative to a less symptomatic comparison group (five-item Mental Health Index Score 86–100), women with depressed mood (score ≤ 52 or clinical depression) showed a significantly greater risk of developing type 2 diabetes (relative risk = 1.17, 95% CI [1.05, 1.30]). Although slightly attenuated, this finding remained significant after adjusting for diabetes-specific covariates such as family history of diabetes and lifestyle factors (e.g., physical activity). Based on further stratification of depression groups, a significant relative risk of 1.25, 95% CI [1.10, 1.41] for developing type 2 diabetes was detected among women taking antidepressants only compared to women classified with either severe depressive symptoms (Mental Health Index score ≤ 52) or physician-diagnosed depression without antidepressants (Pan et al., 2010). A parallel analysis using 7,415 cases of new onset of major depression during a 10-year follow-up period also was conducted to examine the opposite direction of the relationship between depression and type 2 diabetes. Compared to nondiabetic participants, individuals presenting with type 2 diabetes were at significant risk for developing major depression (relative risk = 1.29, 95% CI [1.18, 1.40]; Pan et al., 2010). This finding remained significant even after covariates were

controlled for, including diabetes-specific factors such as physical activity.

Additionally, there is mounting evidence to suggest that the combined effects of depression with type 2 diabetes are associated with a higher risk of all-cause and cardiovascular disease (CVD) mortality in type 2 diabetic patients than in non-depressed diabetic patients (Engum et al., 2005; Katon et al., 2005; Pan et al., 2011). Comorbidity with one or more chronic diseases (e.g., CVD) is shown to be significantly associated with depression in type 2 (*OR* = 1.38, 95% CI [1.10, 1.74]) but not type 1 diabetes (*OR* = 1.28, 95% CI [.76, 2.15]; Engum et al., 2005). Extending this line of research, Pan et al. (2011) examined the associations among depression, type 2 diabetes, and mortality rates in women participating in the Nurses' Health Study. This study was originally established in 1976 and consisted of 121,700 female registered nurses ages 30 to 55 years residing in 11 states. These investigators used the year 2000 questionnaire cycle as a baseline to better understand the risk for mortality in women with depression and diabetes. Women (N = 78, 282) were separated into four categories: (a) neither depression nor diabetes, (b) depression only, (c) diabetes only, or (d) depression and diabetes. CVD-related mortality accounted for 21% of all deaths (n = 979/4,654). On average, women with depression and type 2 diabetes had lower five-item Mental Health Index scores and physical activity levels and higher body mass indexes (BMIs) compared to the other three groups. Relative to women without either condition, the relative risks after controlling for medical comorbidities including heart disease, stroke, and cancer for all-cause mortality were 1.44, 95% CI [1.34, 1.54] for women with only depression, 1.35, 95% CI [1.21, 1.51] for women with diabetes only, and 2.07, 95% CI [1.79, 2.40] for women with both conditions. These findings suggest that the comorbid effect of depression and type 2 diabetes yields more than a two-fold higher risk of mortality in women (Pan et al., 2011). Similar results were found with risk of CVD-specific mortality with a multivariate adjusted relative risk of 2.72, 95% CI [2.09, 3.54] for women with both conditions, which was substantially higher than that found for either depression (1.37) or diabetes (1.67) alone (Pan et al., 2011).

Research findings also suggest that depressed type 2 diabetic patients may be especially vulnerable to the stressors associated with diabetes-specific changes in lifestyle. One study showed that diabetic patients with higher levels of depressive symptoms at baseline reported significantly lower adherence to self-care activities, including general diet recommendations, exercise regimen, and proper foot care at follow-up (β ranging from −.12 to −.23; $p < .05$) (Gonzalez, Peyrot, et al., 2008). Self-care activities for diabetes management place a significant time burden on individuals. Further, adverse side effects of glucose medications and lifestyle disruptions outweigh the long-term benefits of adherence (Rubin, 2005).

These lines of research converge to suggest that depression comorbid with type 2 diabetes is (a) highly prevalent in women; (b) a relationship that is potentially mediated by the role of self-care, including maintaining dietary recommendations and physical activity or other diabetes-specific variables (e.g., family history of diabetes);and (c) a bidirectional association that can inform theories about the underlying mechanism by which depression is linked with diabetes.

Theory

Mechanisms by which depression may be linked to the incidence of type 2 diabetes have been examined within a biopsychosocial framework. Proposed mechanisms include glucose dysregulation, high BMI, and lifestyle (e.g., physical inactivity, poor diet; Everson-Rose et al., 2004). There is evidence to suggest that depression affects glucose metabolism and increased central adiposity (high BMI) via changes to the hypothalamic-pituitary-adrenal (HPA) axis. Alterations in the HPA axis can lead to excess secretion of the stress hormone cortisol, in turn contributing to insulin resistance (glucose dysregulation) and increased fat deposits (high BMI; Everson-Rose et al., 2004).

Additionally, there is research to support the depression-associated insulin resistance mechanism as evidenced in reduced insulin resistance or hyperglycemia following successful treatment of depression. One study showed significant improvement in glycemic control, after controlling for diabetes management and BMI changes, in diabetic patients who were either taking antidepressant medication or receiving cognitive behavioral therapy (CBT) for depression (Lustman, Griffith, Freedland, Kissel, & Clouse, 1998). A more recent study detected a moderate association between depression status at baseline and increased likelihood of developing type 2 diabetes at a 10-year follow-up (relative risk = 1.17, 95% CI [1.05, 1.30]) after adjusting for covariates of physical activity and BMI (Pan et al.,

2010). While it is unclear whether these biopsychosocial factors explain the pathophysiology of depression comorbid with type 2 diabetes, depression in women with type 2 diabetes is highly prevalent and can lead to serious negative outcomes including poor treatment adherence and mortality. To this end, effective recognition and treatment of depression in the context of type 2 diabetes is paramount.

Assessment

Given the psychosocial sequelae and increased burden of disease associated with depression comorbid with type 2 diabetes, depression screening is imperative and should be conducted using well-validated measures. The Beck Depression Inventory–II (BDI–II; Beck, Steer, & Brown, 1996) and the nine-item Patient Health Questionnaire (PHQ-9; Kroenke & Spitzer, 2002) are two of the more frequently used measures for depression screening in both clinical and research contexts. The BDI is the most widely used measure of depression in treatment efficacy research for depression in type 2 diabetic populations (Lustman et al., 1998, 2000). The BDI relies on a patient self-rating of 21 items using a scale from zero to 3 to assess severity of depressive symptoms. In depression screening studies of diabetic patients, a BDI score of 14 or more is shown to have positive predictive values of .57 and .65 for major depressive disorder with rates of depression at 15% and 20% (Lustman, Clouse, et al., 1997). The BDI is well validated in diverse populations and is reliable and sensitive to change in diabetic populations (Lustman et al., 2006).

The PHQ-9 is a nine-item depression scale that consists of the nine criteria for diagnosing *Diagnostic and Statistical Manual of Mental Disorders* (fourth edition; American Psychiatric Association, 1994) major depression, scoring each of the criteria on a scale from 0 (*not at all*) to 3 (*nearly every day*). The PHQ-9 is an effective tool for diagnosing depression, monitoring change in symptoms, and evaluating depression outcomes (Huang, Chung, Kroenke, Delucchi, & Spitzer 2006) and has a high sensitivity (73%) and specificity (98%) for the diagnosis of major depression based on psychiatric interviews (Katon et al., 2004). Finally, use of the PHQ-9 as a depression screening measure is prominent in both epidemiological and treatment efficacy studies targeting depression in type 2 diabetic populations (Katon et al., 2004; Pan et al., 2011; Stoop, Spek, Pop, & Pouwer, 2011).

Another important issue to consider in the assessment of depression comorbidity is the distinction between diabetes-related distress and symptoms of depression (in contrast to a diagnosis of major depression). There is a small body of research to suggest that diabetes-specific distress is associated with poor diabetes treatment adherence and diabetes control, relative to distress linked to symptoms measured by depression screening tools such as the Center for Epidemiologic Studies Depression Scale (Fisher et al., 2010; Radloff, 1977). Measuring symptoms specific to diabetes may inform clinical practice. Nonetheless, even general depressive symptoms are closely related to aspects of diabetes care, as evidenced in reports of higher levels of depressive symptoms in patients on insulin therapy relative to those not taking insulin (Gonzalez et al., 2007). Further, there are data to suggest that objective indicators of diabetes-related issues such as pain, limitations in activities of daily living, and changes in role functioning also are linked to symptoms of depression (Katon et al., 2004). Finally, empirical evidence suggests that the combined effects of diabetes and depression places women at a much higher risk of all-cause and CVD mortality (Pan et al., 2011). Thus to better inform case conceptualization and targeted treatment planning, it is important to assess depression as well as the woman's perspective on how the symptoms are interfering with her daily life.

Treatment

According to a recent meta-analysis, the most common psychological intervention applied to the treatment of depression in type 2 diabetes is CBT (Markowitz, Gonzalez, Wilkinson, & Safren, 2011). Thus far, only one randomized controlled trial investigating the efficacy of CBT for depression comorbid with type 2 diabetes has been completed (Lustman et al., 1998). In this study, all participants were provided individual one-hour diabetes education sessions with a trained diabetes educator every other week. Participants randomly assigned to the active treatment condition also received 10 weeks of individual CBT for depression. The authors reported that 87% of the patients in the CBT group achieved remission (defined as a BDI score <9), which was significantly greater than that of patients in the control group (those receiving education only: 27.3%, $p < .001$). Importantly, 67% of patients in the CBT group achieved *clinically* significant improvement (defined as ≥ 50% reduction in the BDI score), compared to 30% of patients in the control group. At the six-month follow-up assessment, 58% of the patients in the CBT group remained in remission,

which was significantly greater than that for the control group (26%, $p = .03$). This study also assessed blood glucose activity via hemoglobin A1c (HbA1c) levels. Posttreatment analysis revealed no difference in levels between the CBT and control groups; however, at six-month follow-up, participants in the CBT group had significantly lower HbA1c levels (9.5%) relative to participants in the control group (10.9%, $p = .03$).

An uncontrolled study of group CBT for depression in diabetes was conducted to test differences in response to treatment between type 1 and type 2 diabetic patients (Georgiades et al., 2007). In this study, 90 patients with diabetes and depressive symptoms (defined as a BDI score ≥ 10) were enrolled in a 14-week study of group CBT (16 90-minute sessions) with a 12-month follow-up period. The intervention incorporated cognitive restructuring, problem solving, communication, and goal-setting skills specific to diabetes-related thoughts and activities. There was a significant reduction in BDI scores from baseline over the 12-month period ($p < .001$) but no significant changes in HbA1c levels. Even after splitting the sample into subgroups based on high (>8%) and low (<6.5%) HbA1c levels, there was no effect of the intervention on HbA1c levels even in the group that had elevated levels at baseline (Georgiades et al., 2007).

While psychological interventions targeting depression comorbid with type 2 diabetes have yielded significant improvements in depression, the impact of these interventions on treatment adherence is less compelling. Studies testing CBT for depression in the context of diabetes do not specifically address skills to maintain and support treatment adherence (e.g., maintaining self-care).Treatment adherence is important for successful management of diabetes, ultimately preventing adverse diabetes-related outcomes (Gonzalez, Safren, et al., 2008; Katon et al., 2010). Nonetheless, there is evidence to suggest that as depression severity increases in a diabetic population, compliance with self-care behaviors decreases, including adherence to dietary and exercise recommendations and taking medications (Gonzalez et al., 2007). Further, these investigators showed that major depression was strongly associated with poor glucose monitoring (Gonzalez et al., 2007). Thus, treatment of depression in depressed type 2 diabetic patients may not be sufficient for improving diabetes-specific outcomes (e.g., control of blood glucose levels; Gonzalez, Peyrot, et al., 2008; Katon et al., 2004). To this end, efficacious interventions for depression comorbid with type 2 diabetes in women should be integrative and include both depression and behavior management strategies as targets to support treatment adherence (e.g., healthy diet, exercise, glucose monitoring).

Pharmacological interventions also have demonstrated efficacy for treating depression comorbid with type 2 diabetes. A recent meta-analysis identified four published randomized placebo-controlled trials of selective serotonin reuptake inhibitors (SSRIs), one double-blind randomized controlled trial of a tricyclic antidepressant (TCA), and one open-label trial of bupropion (Markowitz et al., 2011). Sertraline is the most commonly prescribed medication for depression in primary care settings (Lustman et al., 2006; Petrak & Herpertz, 2009), with efficacy supported by rigorously controlled double-blind placebo studies using measures of glycemic control (via HbA1c levels) and depressive symptoms (Markowitz et al., 2011).

For example, Lustman et al. (2006) examined the impact of sertraline on the recurrence of depression during a maintenance phase, relative to a placebo; significant effects were detected in a prolonged depression-free interval ($\chi^2 = 5.4$, $p = .02$). At a one-year follow-up, the rate of nonrecurrence was 66% in those receiving sertraline, relative to 48% for those receiving the placebo (Lustman et al., 2006). In an eight-week randomized placebo-controlled trial, fluoxetine was examined as a treatment for depression in type 1 and type 2 diabetic patients (Lustman et al., 2000). Reduction in depressive symptoms was significantly greater in the fluoxetine group, relative to placebo BDI: −14.0 versus −8.8, $p = .03$ and Hamilton Depression Rating Scale: −10.7 versus −5.2, $p = .01$. While findings for glycemic control measured via HbA1c levels were not as promising, there was a trend toward significance in the fluoxetine group (−.40 vs. −.07, $p = .13$; Lustman et al., 2000). In sum, SSRIs have demonstrated efficacy in treating depression with less convincing findings for reducing HbA1c levels. It is unclear whether one SSRI has greater effectiveness over another in reducing symptoms of depression and HbA1c levels in a diabetic population (Markowitz et al., 2011).

The TCAs have generated less research attention. One study examined the effects of a TCA, nortriptyline, on depression and glycemic control in 68 patients (28 of whom had major depression) with type 1 or type 2 diabetes and poor glycemic control (Lustman, Griffith, et al., 1997). A significant reduction in depressive symptoms was detected at the end of treatment in the nortriptyline group,

relative to placebo (BDI: −10.2 vs. −5.8, $p = .03$), with 57% remitting in the treatment group (defined as a BDI score < 10), relative to 36% in the placebo group. The decrease in HbA1c levels was not significant in the nortriptyline condition relative to placebo ($p = .5$; Lustman et al., 1997).

In sum, the current literature supports the utility for both psychological and pharmacological interventions for depression comorbid with diabetes. Further, clinical intervention may be strengthened by an integrative approach that simultaneously targets depression and nonadherence to diabetes management within a behavioral framework. There is growing evidence to suggest that even subclinical depressive symptoms and distress can be associated with worse treatment outcomes. Thus approaches that target symptoms of depression that fall short of a formal diagnosis appear warranted. In these cases, the clinician may find it worthwhile to evaluate whether a case conceptualization that considers these generic depressive symptoms secondary to diabetes-specific factors (e.g., self-care: physical activity, diet) is clinically informative. Regarding pharmacotherapy, while both TCAs and SSRIs improve depression, the SSRIs may be more effective in reducing glucose levels.

Chronic Pain Conditions

Chronic pain is a medical condition affecting more than 50 million Americans, with associated health-care costs and lost productivity of $70 billion annually (Gatchel, 2004). It is loosely defined as persistent or intermittent pain experienced for at least three months (Gatchel, Peng, Peters, Fuchs, & Turk, 2007), with common correlates including depression, fatigue, poor health-related quality of life, and increased health-care utilization (Meana, Cho, & DesMeules, 2004). Depression co-occurring with chronic pain conditions has debilitating effects on an individual's psychological and physical functioning and complicates prognosis and treatment decision making (Hanley, Raichle, Jensen, & Cardenas, 2008). Although depression in chronic pain conditions is experienced by both sexes, most epidemiological and clinical studies show greater prevalence of this comorbidity in women relative to men (Munce & Stewart, 2007; Racine et al., 2012), with fibromyalgia and rheumatoid arthritis having the highest prevalence rates among women (Munce & Stewart, 2007). A national epidemiologic survey ($N = 131,535$) of chronic pain conditions and correlates detected a significant sex × condition association for fibromyalgia with 1.8% of women versus 0.3% of men ($\chi^2 = 134$, $p < .000$) and rheumatoid arthritis with 19.0% of women versus 11.4% of men ($\chi^2 = 283$, $p < .000$; Munce & Stewart, 2007). Women presenting with fibromyalgia reported the highest rates of depression (24%) compared to other conditions (e.g., chronic back pain, migraine headaches), with 11% of women with rheumatoid arthritis reporting depression (Munce & Stewart, 2007). Together, these findings suggest that fibromyalgia and rheumatoid arthritis are important issues to address in the area of women's health and are the focus of this section on chronic pain conditions.

Fibromyalgia

According to the 2010 American College of Rheumatology, a diagnosis of fibromyalgia is based on the following criteria: (a) chronic widespread pain (pain that persists for at least 3 months); (b) at least 11 of 18 tender points on examination; and (c) severity of fatigue, nonrefreshed sleep, cognitive difficulty, and somatic symptoms (Wolf & Häuser, 2011). Fibromyalgia is a debilitating syndrome that mainly affects women (Lawrence et al., 2008) and is highly comorbid with depression (Gabriel & Michaud, 2009; Munce & Stewart, 2007). Most epidemiological studies report a prevalence of fibromyalgia between 2% and 7%, with a female to male ratio of approximately 9:1 (Lawrence et al., 2008). Aside from depression, common manifestations of fibromyalgia include fatigue, lower back pain, joint stiffness, and insomnia, all of which may result in functional impairment (Bennett, Jones, Turk, Russell, & Matallana, 2007) and eventually work disability (Jones, Rutledge, Jones, Matallana, & Rooks, 2008).

In a national survey examining self-reported levels of physical functioning in women with fibromyalgia ($N = 1,735$) using the National Fibromyalgia Association Questionnaire (Bennet et al., 2007), more than 90% reported having difficulty doing heavy household tasks, lifting or carrying 25 pounds, and performing strenuous activities. Further, lower functioning women (based on activities of daily living and instrumental activities of daily living) reported higher levels of pain, spasticity, depression, restless legs, dizziness/fear of falling, and bladder problems, relative to a moderate or high functioning group (Jones et al., 2008). These differences between lower functioning and moderate or high functioning groups may be clinically significant; thus clinicians should consider these symptoms in treatment planning for women identified as lower

functioning in activities of daily living and instrumental activities of daily living. While self-report questionnaires can be used to obtain information regarding fatigue, sleep disturbance, cognitive functioning, and somatic symptoms, an interview-based physical exam and diagnosis by a medical professional (physician, nurse, etc.) should be included in the assessment process.

Rheumatoid Arthritis

Rheumatoid arthritis is a rheumatic disease that is characterized by tender and swollen joints and chronic pain (Pincus, 2007). Rheumatoid arthritis is highly prevalent in women (Crowson et al., 2011) and is associated with an increased risk of depression (Covic et al., 2012). Depression comorbid with rheumatoid arthritis is linked to higher levels of disease activity, pain, fatigue, and poor health related quality of life (Wolfe & Michaud, 2009), as well as overutilization of health-care resources (Covic et al., 2012) and increased risk of mortality (Pincus, 2007). The time of greatest incidence for rheumatoid arthritis is around the age of 60, with incidence rates plateauing after the age of 80 (Crowson et al., 2011). The overall lifetime risk of developing rheumatic disease in U.S. adult women is 8.4%, equivalent to 1 in 12 women (Crowson et al., 2011). In one study examining whether comorbid depression increases mortality in patients with rheumatoid arthritis, after adjusting for covariates, the hazard ratio of clinical depression on mortality was 2.2, 95% CI [1.2, 3.9] (Ang, Choi, Kroenke, & Wolfe, 2005), suggesting that depression increases the risk of mortality in rheumatoid arthritis.

Theory

There is compelling evidence for the application of a biopsychosocial model in understanding the pathways by which depression may be linked to fibromyalgia and rheumatoid arthritis in women (Astin, Beckner, Soeken, Hochberg, & Berman, 2002; Gatchel et al., 2007; Glombiewski et al., 2010; Zautra et al., 2004). Psychosocial factors potentially mediating the association between depression and fibromyalgia and rheumatoid arthritis include cognitive factors (e.g., catastrophizing and depressive self-statements), beliefs, and coping strategies (Bruce, 2008; Hanley et al., 2008; Hassett, Cone, Patella, & Sigal, 2000), with the sympathetic nervous system and the HPA axis representing potential biological factors.

Catastrophizing is a well-studied correlate of depression in chronic pain populations (Gatchel, 2004; Gatchel et al., 2007; Hanley et al., 2008). Catastrophizing is characterized as having pessimistic beliefs about oneself, others, and the future and assuming that the worst possible outcome will occur, leaving individuals feeling helpless and hopeless about their ability to manage internal and external events adequately (Gatchel, 2004). Significant associations between depression and catastrophizing have been detected in female fibromyalgia patients ($r = .71$, $p < .0001$), but not in rheumatoid arthritis patients ($r = .24$, $p = .21$; Hassett et al., 2000). It is notable that in the Hassett et al. study, the duration of illness for fibromyalgia patients was half that of rheumatoid arthritis patients, suggesting that perhaps catastrophizing occurs earlier in the process of accepting an illness. Further, fibromyalgia patients may feel dismissed by their primary care physicians when endorsing symptoms of a condition that is not fully accepted by the health-care community. There was a higher percentage of depressed fibromyalgia patients in this study (44%) relative to rheumatoid arthritis patients (20%). Interestingly, patients presenting with fibromyalgia scored higher on the cognitive subscale of the BDI–II, indicating a higher rate of endorsing depressive self-statements such as "I feel I am a total failure as a person" or "I blame myself for everything bad that happens" (Hassett et al., 2000).

Additionally, there is a body of evidence supporting coping style as a potential underlying mechanism linking depression to fibromyalgia and rheumatoid arthritis in women. In a study examining sex differences in perceived physical self-efficacy (e.g., expectations about one's overall physical capabilities) and task-specific efficacy (e.g., beliefs about one's ability to cope successfully with anticipatory pain), women reported significantly lower levels of perceived self-efficacy, reduced pain tolerance, and increased pain intensity relative to men (Jackson, Iezzi, Gunderson, Nagasaka, & Fritch, 2002). In fibromyalgia, improved self-efficacy has been shown to significantly predict changes in pain and depression, independent of treatment adherence and health status (Burckhardt et al., 1997). Further, the use of denial as a coping mechanism, compared to more active approaches including problem solving, planning, or seeking social support, was associated with depression in rheumatoid arthritic patients (Groarke, Curtis, Coughlan, & Gsel, 2004).

There are several lines of research implicating the role of biological factors in the link between depression and fibromyalgia and rheumatoid arthritis, namely the sympathetic nervous system and HPA

axis (Gatchel et al., 2007). There are data to suggest that pain and fatigue in fibromyalgia may be explained by a chronic, stress-induced blunting of stress response axes, including the sympathetic nervous system and the HPA axis, which may lead to changes in pain regulation processes (Gatchel et al., 2007; Racine et al., 2012). Moreover, there is evidence supporting a link between catastrophizing and the internal experience of chronic stress that triggers physiological responses (e.g., increased heart rate) and the pain process, ultimately increasing the vulnerability to depression in fibromyalgia patients (Hassett et al., 2000). Regarding biological markers in depression comorbid with rheumatoid arthritis, researchers have examined the role of proinflammatory cytokine interleukin-6 (IL-6), a molecule that is produced by immune cells and associated with joint destruction in rheumatoid arthritis patients (Zautra et al., 2008). The production of interleukin-6 also has been shown to be associated with depression (Zautra et al., 2004).

Assessment

Reliable assessment of depression in fibromyalgia and rheumatoid arthritis is critical to the implementation of effective and targeted treatment. Two commonly used scales to examine prevalence rates of depression in rheumatoid arthritis patients are the Depression Anxiety and Stress Scale (Lovibond & Lovibond, 1995) and the Hospital Anxiety and Depression Scale (Covic et al., 2012; Zigmond & Snaith, 1983). The former consists of three 14-item subscales with each item scored on a 4-point Likert scale, ranging from 0 (*did not apply to me at all*) to 3 (*applied to me very much* or *most of the time*). Total scores are calculated by summing the items on each subscale, giving a score range of 0 to 42 on each subscale. Scores above 20 on the depression subscale are indicative of severe levels (Covic et al., 2012). The Depression Anxiety and Stress Scale has good convergent and discriminant validity and high internal consistency and reliability, with Cronbach's alpha reported at. 94 for depression (Covic et al., 2012).

The Hospital Anxiety and Depression Scale was specifically designed to measure both anxiety and depression in outpatient settings, excluding somatic items that may be reflective of the context (i.e., medical condition). The anxiety and depression subscales are comprised of seven items that are rated on a 4-point scale and scored from zero to 3 with total scores ranging from zero to 21 for each subscale. Scores range from 0 to 7 (*no case of anxiety/depression*), 8 to 10 (*possible case of anxiety/depression*), and 11 to 21 (*probable case of anxiety/depression*). These cut points have been validated against clinical interviews with sensitivity and specificity around. 80 (Covic et al., 2012). Recent studies also have yielded adequate internal consistency for both the anxiety (.89) and depression (.86) subscales (Covic et al., 2012).

Regarding assessment of fibromyalgia, one study examined the relations among four methods of detecting depression in female fibromyalgia patients (N = 100): a computerized Diagnostic Interview Schedule, the BDI, an adjusted "disease-free" BDI, and the Minnesota Multiphasic Personality Inventory depression subscale (Burckhardt et al., 1994). Agreement on the diagnosis of depression among the four methods was significantly greater than chance. Compared to the computerized Diagnostic Interview Schedule, the BDI was the most sensitive and specific instrument (Burckhardt et al., 1994).

Treatment

Similar to treatment of depression in type 2 diabetes, treatment of depression comorbid with fibromyalgia and rheumatoid arthritis is challenging for various reasons. First, it is difficult to reliably assess symptoms of depression in the context of disease-specific symptoms. Second, the mechanisms by which depression co-occurs with fibromyalgia and rheumatoid arthritis are unclear. Third, while pharmacotherapy is often a standard treatment across medical conditions, many individuals struggle with adverse side effects associated with medications. Taken together, as discussed in the Treatment section for depression comorbid with type 2 diabetes, an integrative approach to treating depression in fibromyalgia and rheumatoid arthritis may be beneficial for patients.

Research on pharmacological interventions is limited for both conditions. Antidepressants, specifically SSRIs, are considered first-line pharmacotherapy for depression comorbidity (Haüser, Bernardy, Uceyler, & Sommer, 2009; Parker, Hart, & Walker, 2007). A meta-analytic study examining the effects of different classes of antidepressant medications showed a significant overall effect for reductions in the following outcomes for fibromyalgia: pain (standardized mean difference [SMD] = –.43, 95% CI [–.55, –.30]), fatigue (SMD = –.13, 95% CI [–.26, –.01]), depressed mood (SMD = –.26, 95% CI [–.39, –.12]), and health-related quality of life (SMD = –.31, 95% CI [–.42, –.20], with varying results associated with specific antidepressants (Haüser et al., 2009). There

was a significant effect for TCAs (amitriptyline) on reducing pain (SMD = –1.64, 95% CI [–2.57, –.71] and fatigue (SMD = –1.12, 95% CI [–1.87, –.38]), a small effect on improving health-related quality of life (weighted mean difference [WMD] = –.31, 95% CI [–.60, –.01], and a nonsignificant effect on depression (WMD = –.60, 95% CI [–4.53, 3.33]). Additionally, there were small effects for the SSRIs fluoxetine and paroxetine in reducing pain (SMD = –.39, 95% CI [–.77, –.01]), depressive symptoms (WMD = –.37, 95% CI [–.66, –.07]), and improving health-related quality of life (WMD = –.41, 95% CI [–.78, –.05]), with no significant effect on fatigue. There was strong support for the role of duloxetine (serotonin and norepinephrine reuptake inhibitor) in reducing symptoms of depression (SMD = –.26, 95% CI [–.42, –.10]), pain (SMD = –.36, 95% CI [–.46, –.25]) and improving health-related quality of life (SMD = –.31, 95% CI [–.44, –.17]; Haüser et al., 2009). Relatively less substantial data were found for pharmacologic treatment of depression in rheumatoid arthritis. SSRIs are considered to be first-line agents (Parker et al., 2007), with paroxetine having some beneficial effects on somatic pain (Bruce, 2008). Unfortunately, about half of all patients treated with pharmacotherapy experience a 30% reduction of symptoms, suggesting that many patients with depression comorbidity will require additional therapies (Staud, 2010). Further, because of the adverse side effects (e.g., fatigue, weight gain) associated with many medications, patients may want to seek nonpharmacological approaches to treatment (Astin et al., 2002; Hsu, Cherkin, Hoffmeyer, Sherman, & Phillips, 2011). To this end, it may be worthwhile to look to psychological interventions including CBT, mind–body therapies (i.e., mindfulness-based stress reduction [MBSR] programs, exercise, yoga), and self-management strategies to develop multimodal approaches to therapy.

Psychological interventions have been developed to address the psychosocial sequelae of depression in female fibromyalgia and rheumatoid arthritis, including higher levels of depression, pain, and fatigue and lower levels of health-related quality of life. A recent meta-analytic study on psychological treatments for fibromyalgia, including CBT, relaxation, mindfulness-based programs, and education, showed small but significant effect sizes for short-term pain reduction (calculated looking at differences in means from pre- to posttreatment; Hedges' g = .37, [.27, .48]) and depression (Hedges' g = .33, [.20, .45]; Glombiewski et al., 2010). For outcome variables pain intensity, depression, and catastrophizing, psychological treatments were more effective than active control conditions. These treatments generated small to medium effect sizes (pain: Hedges' g = .5; depression: Hedges' g = .44; catastrophizing: Hedges' g = .47; Glombiewski et al., 2010). While all psychological treatments were equally effective in treating depression, CBT outperformed other treatments in short-term pain reduction, a common presenting concern in fibromyalgia and rheumatoid arthritis. Of note, other studies have shown CBT to be comparable to the short-term effects of drug treatment for fibromyalgia (Haüser et al., 2009) and to treatment for other types of chronic pain (e.g., CBT for low back pain; Hoffman, Papas, Chatkoff, & Kerns, 2007). A key component of CBT is focused on helping individuals to recognize and reframe dysfunctional thoughts, including catastrophizing, and to utilize more effective coping strategies (Gatchel et al., 2007). Effective coping is found to be counteractive to feelings of helplessness, which is associated with depression severity and impaired functioning. Further, individuals may gain a sense of self-efficacy and control over illness when learning to cope more effectively with pain (Hassett et al., 2000).

Similar findings were detected in studies on CBT for depression in rheumatoid arthritis (Astin et al., 2002; Zautra et al., 2008). A meta-analytic study showed CBT to be effective for coping with pain and in reducing pain intensity and depression. The effects were strongest for coping (Cohen's d = .46), with more modest outcomes for reducing pain (Cohen's d = –.22) and depression (Cohen's d = –.15; Astin et al., 2002). A more recent study compared the efficacy of CBT for pain with a hybrid mindfulness-based emotion regulation therapy for individuals with rheumatoid arthritis who varied in depression history (Zautra et al., 2008). Both treatments were compared to an education-only group (attention placebo control) in which education about rheumatoid arthritis and other health-related issues was provided. Results showed significantly greater reduction in negative affect (Cohen's d = –.89) and catastrophizing (Cohen's d = –.18) from pre- to posttreatment in those participants with recurrent depression in the mindfulness group relative to participants in the CBT and education groups. Further, participants with recurrent depression in the mindfulness group showed significantly greater improvement in pain coping efficacy (Cohen's d = .65) relative to the CBT and education groups (Zautra et al., 2008).

Mind–body interventions such as mindfulness meditation, relaxation strategies, and yoga also have been investigated as nonpharmacological treatment options for depression in fibromyalgia and rheumatoid arthritis. In fact, mind–body therapies are among the more commonly used treatments by patients with arthritis (Hsu et al., 2011). Mindfulness meditation programs play a prominent role in the chronic pain treatment literature, as evidenced in studies on the efficacy of MBSR (Kabat-Zinn, Lipworth, & Burney, 1985) for chronic back/neck pain, headaches, arthritis, and fibromyalgia (Grossman, Tiefenthaler-Gilmer, Raysz, & Kesper, 2007; Rosenzweig et al., 2010; Sephton et al., 2007). MBSR interventions integrate aspects of mindfulness, grounded in Buddhist philosophy, with yoga poses (Kabat-Zinn et al., 1985). There are many forms of mindfulness meditation. In the context of an MBSR program, the focus is on practicing mindful awareness by paying attention to thoughts purposefully and nonjudgmentally (Kabat-Zinn, 1990).

Two studies have tested the effects of MBSR on reducing depressive symptoms in females with fibromyalgia. In one study, a standard MBSR program significantly reduced depressive symptoms, relative to a waitlist control group, in female fibromyalgia patients ($F(1, 87) = 12.02$, $p < .001$; Sephton et al., 2007). The second study was conducted using a quasi-randomized design with 39 female fibromyalgia patients receiving MBSR and 13 patients assigned to an active control group to account for the nonspecific effects of MBSR. Results revealed strong effects in the MBSR group, relative to the active control, on measures of health-related quality of life (Cohen's *d*s = .52–1.12), pain (Cohen's $d = 1.10$), depression (Cohen's $d = .39$), and coping abilities (Cohen's *d*s = .34–.88) (Grossman et al., 2007). Importantly, in an observational three-year follow-up study, MBSR participants maintained treatment gains in these domains compared to preintervention status (Grossman et al., 2007).

MBSR programs have been effective for depression in rheumatoid arthritis as well. One study showed that following completion of an MBSR intervention, arthritis patients showed significant improvements on the anxiety and depression subscales of the Symptom Checklist-90-Revised (Cohen's $d = .87$ and Cohen's $d = .88$, respectively; Rosenzweig et al., 2010). These findings are somewhat consistent with an earlier study examining the effects of an MBSR program on psychological outcomes in women with rheumatoid arthritis (Pradhan et al., 2007). The design of this study included a standard eight-week MBSR program and a maintenance program in which participants attended three refresher classes during a four-month continuation period, with a final assessment made six months post-baseline. The Symptom Checklist-90-Revised was used to evaluate depressive symptoms, psychological distress, and well-being. While significant findings were not detected at two months posttreatment, a significant improvement in psychological distress, $F(1, 56) = 4.02$, $p = .04$, and well-being, $F(1, 56) = 5.23$, $p = .03$, was detected for the MBSR group at the six-month assessment, relative to the waitlist control group. There was a trend toward significant treatment effects in depression, $F(1, 56) = 3.16$, $p = .08$, with no significant impact on rheumatoid arthritis disease activity at the six-month assessment (Pradhan et al., 2007).

Yoga also has been examined in the context of mind–body interventions. The beneficial effects of yoga are manifold. Through the practice of various poses, individuals realize that they can be physically active despite pain symptoms (e.g., acceptance rather than avoidance of pain) and experience higher levels of self-efficacy, both of which are linked to improved quality of life (McCracken & Vowles, 2008). Empirical studies have detected positive effects of yoga interventions on pain and psychological functioning in rheumatoid arthritis patients (Haaz & Bartlett, 2012). Although preliminary, a nonrandomized controlled trial examining yoga for rheumatoid arthritis in postmenopausal women showed a significant improvement in pain and depression (Bosch, Traustadottir, Howard, & Matt, 2009). Further, based on a recent meta-analysis, yoga interventions were efficacious in reducing symptoms of depression in women presenting with fibromyalgia (Langhorst, Klose, Dobos, Bernardy, & Haüser, 2013). This study combined various modalities, including Qigong, Tai Chi, and yoga, to form what the authors classified as meditative movement therapies. Overall, these therapies were shown to significantly reduce sleep disturbance, fatigue, depression, and limitations of health-related quality of life at posttreatment relative to controls (Langhorst et al., 2013). Of note, in a subgroup analysis, yoga was the only modality yielding significant effects on the following outcomes at posttreatment: pain (SMD = –.54, 95% CI [–.96, –.11]), fatigue (SMD = –1.02, 95% CI [–1.47, –.58]), depression (SMD = –.78, 95% CI [–1.22, –.35]), and health-related quality of life (SMD = –.92, 95% CI [–1.42, –.41]).

In sum, the standard treatment protocol for depression comorbid with rheumatoid arthritis and fibromyalgia should involve both assessment and a multimodal approach to therapy. Use of a psychometrically robust depression screening measure is important. The BDI–II is a reliable instrument and has the ability to assess both vegetative and cognitive symptoms of depression. Various pharmacologic agents have demonstrated efficacy in reducing symptoms of pain, depression, and fatigue and improving health-related quality of life in fibromyalgia with little evidence supporting pharmacotherapy for depression in rheumatoid arthritis. Nevertheless, pharmacotherapy is often associated with adverse side effects and poor adherence; thus it should be considered only one piece of the puzzle in effective management of depression comorbidity, if at all. Findings from several studies converge to lend support for the effectiveness of CBT and mind–body interventions, including MBSR programs and yoga. The effectiveness of CBT across both conditions lends support to the previously discussed theory on the role of catastrophizing as a coping style linking depression with fibromyalgia and rheumatoid arthritis. Careful assessment of both mood and coping styles for patients with fibromyalgia and rheumatoid arthritis will inform the development and application of targeted and efficacious treatments.

Future Research Directions

There is a well-established literature on the epidemiology and biopsychosocial correlates of depression comorbid with type 2 diabetes, fibromyalgia, and rheumatoid arthritis in women. Psychosocial interventions for these conditions, however, could benefit from further investigation. Regarding treatment efficacy research, studies with longer follow-up periods should be conducted to better understand the role of relapse and recurrence. For example, findings from a meta-analysis on the effects of CBT for depression showed that following discontinuation of acute-phase treatment, 29% of responders (N = 1,880 adults) had a relapse/recurrence within one year and 54% had one within two years (Vittengl, Clark, Dunn, & Jarrett, 2007). Further, these meta-analytic findings suggest that continuation phase treatments can reduce relapse/recurrence significantly, relative to nonactive comparison groups (e.g., assessment only) and other active-continuation phase treatments (e.g., pharmacotherapy; Vittengl et al., 2007). Extending the follow-up period and incorporating relapse-prevention strategies such as continuation-phase treatments that match the modality used in the acute phase into study designs may address issues surrounding relapse and recurrence. Second, intervention research should include multisite trials to generate adequate sample sizes that will allow for stronger tests of efficacy for the outcomes of interest (e.g., depression, pain, fatigue, health-related quality of life), as well as for the investigation of individual differences, including gender, age, sociodemographics (e.g., ethnicity and economic status), and treatment preferences. Third, the less-established psychosocial interventions should be tested against the more rigorously tested interventions, including CBT and antidepressants, to examine whether one yields incremental efficacy and acceptability. Scientific investigation into mind–body interventions such as yoga is in its infancy. Thus current outcome studies are relatively small in size and scope relative to the more robustly designed CBT and antidepressant studies. Future studies examining the efficacy of mind–body interventions for chronic medical conditions in women could be improved upon by the following: (a) including additional treatment arms (e.g., CBT, pharmacotherapy), (b) clarifying the intervention delivered (e.g., style of yoga, poses, treatment manual), and (c) including well-described design methods and analyses to facilitate replication studies (Haaz & Bartlett, 2012). Fourth, dismantling studies for psychosocial interventions should be conducted to investigate hypothesized mechanisms of action (e.g., mediators) for the respective treatment modality. Finally, patient characteristics associated with positive and negative outcomes should be examined as moderators to more effectively target interventions.

Summary

This chapter provides an overview of the literature on depression comorbid with type 2 diabetes, fibromyalgia, and rheumatoid arthritis in women. The epidemiology, theory, assessment, and treatment of depression comorbid with these chronic medical conditions in women were discussed to improve understanding of the role of clinicians in assessing and managing depression comorbidity. It is clear that (a) the prevalence of depression in women with type 2 diabetes, fibromyalgia, and rheumatoid arthritis is high and can lead to declines in psychological and physical functioning; (b) universal screening of depression in women presenting with these conditions is critical; and (c) a

multimodal approach should be considered to effect change in treatment outcomes. Interventions for these comorbid conditions should be integrative, combining empirically supported psychological treatments with interventions that address health behaviors and treatment adherence. This multimodal approach will address not only the depression but also may have a positive effect on health outcomes. Currently, there is a gap in the literature on integrative approaches to treating depression comorbid with the women's health issues discussed in this chapter. Future intervention research should focus on developing integrative approaches that target the depression and associated sequelae (e.g., poor treatment adherence and health-related quality of life), ultimately effecting change on a broader level by decreasing health-care utilization and direct health-care costs. Additionally, consideration should be given to including longer follow-up periods that integrate continuation-phase treatments to address issues of relapse/recurrence. Various clinicians, health-care practitioners, and mental health experts are instrumental in administering screening measures to assess for depression and in applying evidence-based multimodal interventions for depression comorbid with women's health issues, in turn improving the mental health and quality of life in women.

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CHAPTER

28 Intimate Relationships

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Abstract

The concurrent and longitudinal association between intimate relationship dysfunction and depression is well established in both adolescents and adults. This association can be best understood as a bidirectional transactional one, such that intimate relationship dysfunction and depression reciprocally influence one another over time. This chapter reviews the existing research in this area, focusing on the main components and processes of intimate relationships (including how they start, function, and end) in relation to depression. Adolescent research has also focused on how romantic and sexual experiences relate to depression, which is also reviewed. Finally, couple therapy, particularly cognitive behavioral couple therapy, is discussed as an efficacious treatment for comorbid intimate relationship dysfunction-depression. Future directions for research are also suggested.

Key Words: depression, intimate relationship dysfunction, comorbidity, adolescent research, romantic experiences, sexual experiences, couple therapy

Introduction

Depression is a devastating psychological disorder that has both intrapersonal and interpersonal consequences. For example, in addition to the personal suffering associated with the disorder, depression significantly affects the relationships of depressed individuals, particularly intimate relationships. Intimate relationships play a central role in most people's lives, and over 90% of people in the United States get married (Kreider & Fields, 2001). However, approximately 30% of married individuals in the United States can be classified as being in discordant relationships (Whisman, Beach, & Snyder, 2008) and nearly 50% of marriages end in separation or divorce (Kreider & Fields, 2001). Given the negative interpersonal consequences of depression and the relatively high rates of people in dissatisfied intimate relationships, it is critical to understand the comorbidity between depression and intimate relationship dysfunction so as to improve individuals' personal well-being and relationship functioning. In this chapter, we present an overview of the literature on depression in intimate relationships, describe theoretical models and treatment strategies, and provide future directions for research. In addition to the adult literature, we review the link between adolescent romance and depression. Because most work on the association between intimate relationships and depression has focused on adults, we begin with the adult literature and review the adolescent literature separately.

Depression and Intimate Relationship Dissatisfaction

Research has consistently demonstrated cross-sectional associations between marital dissatisfaction and depressive symptoms in community and clinical samples (for a review, see Whisman, 2001a). Furthermore, spouses of depressed individuals also report greater marital dissatisfaction

(e.g., Sacco, Dumont, & Dow, 1993). Whisman's (2001b) meta-analysis obtained medium to large effects for the cross-sectional association between marital dissatisfaction and depressive *symptoms* (women: $r = .42$; men: $r = .37$) and large effects for diagnosable depression ($r = .66$). Marital dissatisfaction accounted for 14% to 18% of the variance in depressive symptoms and 44% of the variance in diagnosable depression. Thus, concurrent associations between relationship satisfaction and both depressive symptoms and diagnoses are well documented. Moreover, it is generally accepted that the association is reciprocal, such that depression leads to romantic dysfunction and romantic dysfunction also leads to depression. Next, we review evidence documenting this bidirectional association.

Relationship Dysfunction as a Precursor to Depression

In accord with models of depression–relationship dysfunction comorbidity wherein relationship dysfunction acts as a precursor to depression (e.g., Beach, Sandeen, & O'Leary, 1990), retrospective reports suggest that depressed individuals tend to believe that their marital dissatisfaction preceded their depressive symptoms (e.g., O'Leary, Riso, & Beach, 1990). More recently, prospective studies show that marital dissatisfaction predicts increases in depression (e.g., Beach & O'Leary, 1993; Beach, Katz, Kim, & Brody, 2003). In fact, Kendler and colleagues (1995) found that serious marital problems were associated with approximately an 8- to 14-fold increase in risk for onset of major depressive disorder (MDD). Moreover, other work indicates that dissatisfied spouses (who were not depressed) were nearly three times more likely than satisfied spouses to develop a major depressive episode (MDE) during the year (Whisman & Bruce, 1999). Additionally, nearly 30% of the new occurrences of MDEs were associated with marital dissatisfaction. This finding has been replicated in independent epidemiologic studies, with results suggesting that marital discord is associated with increased risk for first incidence and total incidence of MDD and dysthymia (Overbeek et al., 2006) and spousal problems are associated with increased risk for onset of MDD (Wade & Kendler, 2000). In a study unique in its focus on the stability of relationship satisfaction, findings suggested that women whose relationship satisfaction fluctuated more widely evidenced higher depressive symptoms 12 weeks later (Whitton & Whisman, 2010). Notably, instability in relationship satisfaction accounted for unique variance in depressive symptoms, suggesting that such instability may promote depressive symptoms independently of level of relationship satisfaction.

Depression as a Precursor to Relationship Dysfunction

Conversely, it has been theorized that depression may precede relationship dysfunction (e.g., Coyne, 1976). Supporting this, depressive symptoms have been found to predict increases in marital dissatisfaction over the course of 15 months in a community sample of men (Ulrich-Jakubowski et al., 1988) as well as lower levels of relationship quality over the course of 15 years in a large sample of mothers (Papp, 2010). Also, diagnosable depression during adolescence is associated with greater marital dissatisfaction during early adulthood (Gotlib, Lewinsohn, & Seeley, 1998). Two other studies demonstrated that depression is associated with changes in relationship quality over time, but their results conflicted in regard to gender. Fincham and Bradbury (1993) found that women's depressive symptoms predicted increases in their marital dissatisfaction over time, whereas men's marital dissatisfaction predicted increases in their depressive symptoms over time (i.e., the associations were significant in different causal directions depending on gender). In contrast, Fincham and colleagues (1997) showed that men's depressive symptoms predicted increases in their marital dissatisfaction over time, but women's marital dissatisfaction predicted increases in their depressive symptoms over time. Despite some inconsistencies, these findings suggest that depression predicts increases in romantic dysfunction.

Depression and Relationship Dysfunction as a Reciprocal Process

As noted, it is generally accepted that there is a reciprocal relationship between depression and relationship dysfunction. This bidirectional relationship has been demonstrated in several studies, including some among first-married women and men over the first four years of marriage (Kurdek, 1998) and first-married women (but not men) over the first year of marriage (Davila, Bradbury, Cohan, & Tochluk, 1997). Two studies have replicated this bidirectional relationship using growth curve analyses (Davila et al., 2003; Karney, 2001), suggesting that the depression–relationship dysfunction link operates at the individual as well as the group level. Both studies demonstrated that if a particular individual's depressive symptoms decreased from one

assessment to the next, that individual was also likely to experience a decrease in marital satisfaction. Notably in both studies, the strength of the relationship did not differ as a function of the direction of the relationship. Other work suggests there may be a bidirectional link between depression and marital satisfaction for women but not men. For example, in a sample of newlyweds, depressive symptoms predicted increases in marital dissatisfaction for both partners, but marital dissatisfaction predicted increases in depressive symptoms for wives only (Dehle & Weiss, 1998). These findings provide evidence to support the bidirectional relationship between depression and intimate relationship dysfunction, at least among married couples.

Course: First Onsets, Recurrences, Recovery, and Relapse

Research on the role of relationship dysfunction in the course of depression is limited. Emerging evidence suggests that romantic dysfunction may be associated with first onsets of depression. For instance, in a large international sample, being married (versus having never been married) was associated with reduced risk of first onset of MDD or dysthymia for men but not women. Further, having been previously married (versus being in a first marriage that has remained intact) was associated with increased risk of first onset of MDD or dysthymia for both women and men (Scott et al., 2010). In terms of recurrences, results from one study suggested that those who experienced recurrent MDEs during a 10-year period following release from an inpatient hospitalization were significantly more likely to be dissatisfied with their intimate relationships or to have experienced a marital separation compared with those who did not experience recurrences (Kronmüller et al., 2011). Thus emerging evidence suggests that relationship dysfunction is associated with first onsets and recurrences; but whether romantic dysfunction is differentially associated with first onsets versus recurrences remains a question for future research (cf. Monroe, Rohde, Seeley, & Lewinsohn, 1999).

There is also some limited evidence to suggest that romantic dysfunction is associated with depressive relapse. Hooley and colleagues (e.g., Hooley & Teasdale, 1989) showed that marital distress and spousal criticism (both perceived and observer-rated) are associated with depressive relapse. Additionally, in the Treatment of Depression Collaborative Research Program, poor marital adjustment at posttreatment predicted greater depressive symptoms at follow-up (Whisman, 2001b). Finally, evidence suggests that marital satisfaction is associated with subsequent remission (Moya, Prous, Fernandez, & Alonso, 2010). Thus accumulating evidence indicates that romantic dysfunction is associated with depressive relapse and poorer recovery from depressive episodes.

Gender Differences

Gender has received a great deal of attention as a potential moderator of the depression–romantic dysfunction relationship, given that women are approximately two times more likely to experience depression (e.g., Nolen-Hoeksema, 1987). In line with this, some studies find that depression and relationship satisfaction are more strongly associated for women than men (e.g., Dehle & Weiss, 1998; Fincham et al., 1997), but other studies do not (e.g., Beach et al., 2003; Davila et al., 2003). In his meta-analysis, Whisman (2001b) found that the association between marital dissatisfaction and depressive symptoms was significantly stronger for women that for men, but this difference was small (women: $r = .42$; men: $r = .37$). Thus, if the association is stronger for women than men, the difference does not appear to be very large.

Specificity

In population-based studies, marital dysfunction is associated with a range of mood, anxiety, and substance use disorders (e.g., Overbeek et al., 2006; Whisman, 1999, 2007), leading to questions about whether marital dysfunction is a risk factor for psychopathology in general. Although marital dysfunction appears to be a risk factor for various types of psychopathology, there is some evidence that its associations with certain types of psychopathology are particularly robust. For instance, marital dissatisfaction was associated with numerous disorders in the National Comorbidity Survey, but it was *uniquely* related only to MDD and posttraumatic stress disorder for women and to dysthymia for men (Whisman, 1999). Further, Whisman and colleagues (2006) demonstrated that the link between marital discord and depressive symptoms remains even when controlling for aspects of well-being and personality.

Interestingly, research on the specificity of the relationship dysfunction–psychopathology link has begun to incorporate novel perspectives on the classification of psychopathology. In their examination of the association between marital discord and the broad dimension of internalizing symptoms, Brock

and Lawrence (2011) revealed that marital discord was prospectively associated with internalizing symptoms over the first seven years of marriage for men but not for women. Similarly, other work suggests that higher internalizing and higher externalizing psychopathology are both associated with lower general marital adjustment for husbands and wives (South, Krueger, & Iacono, 2011). Furthermore, there were no residual associations between any specific mental disorder and overall relationship adjustment after controlling for the broad dimensions of internalizing and externalizing psychopathologies, suggesting that marital distress may reflect an inability to regulate emotions central to internalizing psychopathology and/or the tendency to project distress outward central to externalizing psychopathology.

Comorbid Depression–Romantic Dysfunction in Adults: Impact on Work and Friends

Although research has not directly addressed the impact of comorbid depression and relationship distress on work and friends, indirect evidence speaks to their interconnections. First, depression and relationship distress are both associated with impairment in social and occupational functioning (e.g., Whisman & Uebelacker, 2006). Second, interpersonal models of depression suggest that depression will lead to dysfunction across relationships, including romantic relationships and friendships (e.g., Coyne, 1976; Hammen, 1991). Indeed, the effects of stress generation contribute to interpersonal stressors outside of the relationship and may be amplified by qualities of the relationship (e.g., Trombello et al., 2011). Finally, findings from investigations of spillover effects indicate that stress from one domain (e.g., work, marriage) bleeds into other domains. For example, Brock and Lawrence (2008) demonstrated that escalating role strain outside of the marriage (e.g., friendships, work/school) predicted greater increases in marital dissatisfaction over time for husbands but not wives (who appeared to be protected by their husbands' social support). Thus evidence suggests that meaningful associations exist among depression, relationship distress, and impairment in friendships and work performance, although these relationships have not been directly evaluated.

Research on Comorbidity and Specific Relationship Processes

In this section, we focus on the main processes and components of couple relationships and their associations with depression.

Depression and Relationship Formation

Although research has not directly examined whether depression is associated with relationship formation, there are some findings suggesting that a history of depression or current depression may have implications for relationship formation. For instance, those who are in serious relationships or married exhibit lower rates of depression compared with individuals who are not in serious relationships or married (for a review, see Umberson & Williams, 1999). This may mean that romantic relationships serve as a protective factor to the development of depression. Indeed, some studies have followed individuals over time and found that those who transition to marriage as compared with those who remain single have less depression, even after controlling for initial levels of depression (Horwitz, White, & Howell-White, 1996; Kim & McKenry, 2002). Conversely, marriage may be associated with lower rates of depression because depressed adults are less likely to enter into or remain in romantic relationships than nondepressed individuals. In support of this, some work indicates that depressed women are less likely to marry over long-term follow-up periods (Horwitz et al., 1996; Papp, 2010). Together, these findings suggest that depressed individuals may be less likely to form or maintain a relationship, or perhaps romantic relationships protect individuals from developing depression.

In contrast, some studies indicate that women who experience depression in adolescence or early adulthood may marry at an earlier age (e.g., Gotlib et al., 1998; Kessler, Walters, & Forthofer, 1998), consistent with research on depression and adolescence, which we discuss further below. It has also been argued that the lower rates of depression evidenced by those in relationships may reflect the distress that accompanies a divorce or separation rather than remaining single (e.g., Whisman, Weinstock, & Tolejko, 2006). Consistent with this, studies comparing married and never married individuals reveal that never married people are less depressed (Romanoski et al., 1992) or show no difference in depression rates (e.g. Kessler et al., 2003). These findings are intriguing, given that research has documented a link between romantic involvement and depression in adolescence; this suggests that dysphoric adolescents are at risk for entering into relationships that have the potential to maintain their depressive symptoms.

Depression and Relationship Satisfaction

As described, the association between depression and relationship dissatisfaction is well established

(e.g., Whisman, 2001a). As such, research has focused on identifying factors that strengthen the association. For example, research suggests that marital dissatisfaction may be more strongly associated with increases in depressive symptoms for partners with higher neuroticism (Davila et al., 2003), an anxious-ambivalent attachment style (Scott & Cordova, 2002), lower self-esteem (men only) (Culp & Beach, 1998), and higher blame-oriented attributions about the partner's negative behaviors (i.e., believing their partner intentionally and selfishly engaged in negative behavior to hurt them; Gordon, Friedman, Miller, & Gaertner, 2005). Also, relationship status and length may be important factors to consider. For instance, the depression–marital dissatisfaction link was stronger for husbands but not wives in longer relationships (Kouros, Papp, & Cummings, 2008). Similarly, relationship dissatisfaction was more strongly associated with current MDD for married individuals as compared with cohabitating individuals (Uebelacker & Whisman, 2006). Interestingly, neuroticism amplified the concurrent link between marital dissatisfaction and MDD for married but not cohabitating individuals. However, other demographic (e.g., gender, race/ethnicity) and family-of-origin variables (e.g., parental divorce) did not affect the association regardless of marital status (Uebelacker & Whisman, 2006; cf. Whisman, 2001b).

Elucidating the mechanisms underlying the link between satisfaction and depression has also been a focus of recent work. For instance, self-silencing behaviors mediated the concurrent and longitudinal associations between marital dissatisfaction and depressive symptoms among wives but not husbands (Du Rocher Schudlich, Papp, & Cummings, 2011; Uebelacker, Courtnage, & Whisman, 2003). Moreover, conflict resolution styles partially mediated the prospective link between marital dissatisfaction and depression (Du Rocher Schudlich et al., 2011). Together, this work suggests that dissatisfaction may lead to overengagement (conflict) or underengagement (self-silencing), which in turn leads to depression.

Depression and Relationship Functioning

Depression is also associated with poor relationship functioning in a variety of domains. For instance, as compared with nondepressed wives, depressed wives exhibit more negative behaviors while solving problems, including voicing complaints, making self-derogatory statements, whining, and having a depressed attitude regardless of level of marital satisfaction (Jackman-Cram, Dobson, & Martin, 2006). Also, spouses of current and remitted depressed women report greater use of coercive problem-solving tactics than spouses of nondepressed individuals (Hammen & Brennan, 2002).

The interactions and communication patterns of couples with a depressed partner are also more negative. For example, depressed individuals perceive their interactions to be more negative and report lower satisfaction with their communication than nondepressed individuals (Basco, Prager, Pita, Tamir, & Stephens, 1992). Husbands of depressed wives also report giving and receiving fewer expressions of affection, more destructive coping, and more marital complaints as compared with husbands of nondepressed individuals (Coyne, Thompson, & Palmer, 2002). Moreover, observational data suggest that couples with a depressed partner exhibit more negative and less positive behaviors and greater levels of hostility (e.g., for a review, see Rehman, Gollan, & Mortimer, 2008). Interestingly, sequential analyses revealed that when depressed husbands exhibited positive behavior, it was followed by decreased positivity and increased negativity from wives (Johnson & Jacob, 2000). Conversely, other work indicates that when depressed wives displayed a depressive behavior, their husbands were less likely to respond with a negative behavior (Hops, Biglan, Sherman, Arthur, Friedman, & Osteen, 1987). Research has also explored the mechanisms by which negative interactions may promote depression. For example, in a study of married couples, negative marital interactions were associated with subsequent decreases in relationship confidence, which, in turn, predicted increases in depression (wives only; Whitton et al., 2007).

One aspect of communication that has been particularly prominent in the literature is criticism of depressed individuals by romantic partners. Numerous studies have demonstrated that husbands of depressed women (compared to husbands of nondepressed women) rate their wives more negatively on a variety of traits, both related and non-related to depression (e.g., Sacco, Dumont, & Dow, 1993), even when their depression is remitted (Levkovitz, Lamy, Ternachiano, Treves, & Fenning, 2003). Partner criticism may be especially important in terms of depressive relapses and recurrences. Hooley and Teasdale (1989) found that a depressive relapse was associated with both marital distress and spousal criticism. Interestingly, findings indicated that perceived levels of partner criticism may be more important than actual levels of partner

criticism in predicting relapse. This highlights the role of negative thinking patterns in increasing vulnerability to depression, suggesting that individuals' negative perceptions of their partners' behavior may play a role in relapse.

Similarly, lack of support from a partner predicts increased risk for the onset of depression (e.g., Wade & Kendler, 2000). Marital support may be especially important in couples with children, as one study revealed that increases in marital support lead to greater decreases in depressive symptoms for parents of young children as compared with nonparents or parents of adult children (Beam et al., 2011). Conversely, it appears that depression also contributes to deficits in social support skills, which in turn, leads to increases in marital stressors, exacerbating depressive symptoms over time (Davila et al., 1997). Social support behaviors also affect relationship functioning and satisfaction. In a study of newlyweds, low levels of observed positive support behaviors and high levels of observed negative support behaviors predicted increased displays of negative emotions during problem-solving tasks one year later (Sullivan, Pasch, Johnson, & Bradbury, 2010). Furthermore, the couples evidencing poorer social support skills had lower relationship satisfaction and were more likely to divorce over the first 10 years of marriage. Taken together, these findings suggest that social support plays a key role in the bidirectional association between romantic dysfunction and depression.

Finally, negative relationship events, especially those associated with betrayal or humiliation, predict onsets of major depression. For instance, data from a community sample of discordant married women found that wives who had recently experienced a husband-initiated separation or a husband's infidelity were at significantly higher risk of experiencing a subsequent MDE than wives who were unhappy in their relationship but had not experienced a humiliating marital event (Cano & O'Leary, 2000). In sum, research on relationship functioning shows that relationships with a depressed partner are more likely to have various problems in adaptive functioning, which influences both the course of depression and relationship outcome.

Depression and Relationship Dissolution

It is well-established that divorce and relationship separation confer significant risk for depression even after controlling for a variety of confounding factors (e.g., Gibb, Fergusson, & Horwood, 2011). Individuals who are divorced, separated, or widowed have higher rates of depression and are at a greater risk of becoming depressed than married individuals (e.g., Kessler et al., 2003). Similarly, the dissolution of a cohabitating relationship may confer similar risk for subsequent depression (Overbeek, Vollebergh, Engels, & Meeus, 2003).

At the same time, depression is associated with subsequent divorce and relationship dissolution. For example, individuals with a history of MDD spend fewer years married in adulthood (Kessler et al., 1998) and are more likely to divorce, with one study demonstrating that those with a history of MDD were 70% more likely to separate or divorce within the upcoming year than those without a history of MDD (Bruce, 1998). Even the experience of depression in childhood or adolescence can have implications for future adult relationships. For instance, Jonsson and colleagues (2011) found that women who had experienced a MDE during adolescence had a higher risk of divorce and single parenthood 15 years later than women who did not have a history of adolescent depression.

Together, these findings suggest that the connection between depression and relationship dissolution is bidirectional. The effects of depression may lead to relationship dysfunction to the point of dissolution, but experiencing the end of a romantic relationship may also lead to subsequent depression. In line with this, in the Canadian National Population Health Survey, depression was associated with twice the proportion of transitions from common-law or married to separated or divorced status; also, an increased proportion of nondepressed individuals with separated or divorced status subsequently experienced MDD (Bulloch, Williams, Lavorato, & Patten, 2009). Notably, for some individuals, staying in an unhappy relationship may be associated with depression. Davila and Bradbury (2001) showed that individuals who stayed in unhappy marriages had higher levels of depressive symptoms at the beginning of and during their marriages as did individuals who remained married or divorced during a four-year period. Findings from another study revealed that individuals in distressed relationships who separated from their partners had a fivefold increased probability of recovering from MDD and no increased probability of relapsing following the separation (Cohen, Klein, & O'Leary, 2007). Thus, at least for some individuals, depression may be associated with staying in an unhappy relationship; therefore leaving a discordant relationship may actually alleviate rather than precipitate depression.

Theories: Comorbid Depression and Romantic Dysfunction in Adults

As the research reviewed previously attests, the bidirectional transactional link between relationship dysfunction and depression is robust. In this section, we present theoretical models to guide our understanding of this work.

Coyne's Model

Coyne's (1976) interactional theory of depression proposes that mildly depressed individuals attempt to alleviate feelings of guilt and low self-worth by seeking reassurance from others, including their romantic partners. Initially, others provide reassurance, but depressed individuals doubt its veracity and thus continue to seek it, eventually frustrating others and eliciting rejection. This creates a cycle in which depression and interpersonal dysfunction reciprocally influence one another, setting up an interaction between the depressed person and his or her partner that serves to maintain and exacerbate depression over time.

Stress Generation

Hammen's (1991) stress generation model posits that depressed individuals and those with a history of depression contribute to the occurrence of stress in their lives, which serves to exacerbate their depression over time. Applied to romantic relationships, stress generation theory suggests that depressed partners contribute to stressful relationship experiences (e.g., conflict) that serve to maintain or increase the depressed partner's depression over time. Davila and colleagues (1997) demonstrated support for this model in newlywed women but not men. Dysphoric wives were more negative and critical when attempting to receive and provide support to their husbands in an objectively coded marital interaction, which in turn was associated with prospective increases in marital stress, leading to further increases in depressive symptoms. These findings suggest that negative or ineffective social support may be one mechanism of marital stress generation in women. Other research suggests that different aspects of marital functioning may affect stress generation processes for wives and husbands, at least when stressors outside of the marriage are considered. For instance, findings from a longitudinal study of newlyweds indicate that for husbands, stress generation effects were moderated by behaviors observed in couples' social support and problem-solving interactions (e.g., infrequent positive affect) but not relationship satisfaction. However, for wives, stress generation effects were moderated by relationship satisfaction (effects were more evident when satisfaction was low as opposed to high) but not interaction behaviors (Trombello, Schoebi & Bradbury, 2011). Together these findings suggest that stress generation in the context of marital relationships may operate differently for men and women.

Notably, recent conceptualizations of the stress generation theory have distinguished between two potential theoretical interpretations of the stress generation model (Uliaszek et al., 2012). First, consistent with existing research on marital stress generation (e.g., Davila et al., 1997), in stress causation, characteristics of depressed individuals contribute to the generation of stress over time. Second, in stress continuation, the prospective relationship between stress and depression is due to the stability of stress over time rather than a causal relationship between depression and future stress. The latter has yet to be tested in the context of romantic relationships but has received support in a sample of late adolescents (Uliaszek et al., 2012). This initial work compels a test of the stress continuation model in romantic relationships, as it may be that those with a history of depression manifest consistently elevated levels of chronic stress in their relationships (e.g., high conflict, low support, low trust; supporting stress continuation); therefore depression may not predict increases in levels of chronic stress once accounting for initial levels of chronic stress (contradicting stress causation).

Marital Discord Model of Depression

The marital discord model of depression (Beach, Sandeen, & O'Leary, 1990) proposes that marital processes and depressive symptoms reciprocally influence one another, creating a vicious cycle that serves to maintain or exacerbate both discord and depressive symptoms over time. Specifically, the model posits that marital discord is manifested by decreases in support provision (e.g., spousal dependability, cohesion) as well as increases in chronic, negative, and threatening stressors (e.g., verbal and physical aggression, threats of separation or divorce), leading to subsequent depression, which is then manifested in further maladaptive behaviors (e.g., conflict avoidance, interpersonal friction) and, ultimately, further marital discord. Longitudinal studies testing this model have produced inconsistent findings, but this work has rarely tested the mechanisms (increased relationship stress and decreased support) proposed by the model. In exception to

this, in a longitudinal study of married couples, angry, depressive, and constructive styles of conflict partially mediated the link between marital dissatisfaction and subsequent depressive symptoms, although effects varied by gender. For instance, husbands' constructive conflict behavior mediated the marital dissatisfaction-depression link for wives but not husbands (Schudlich Du Rocher et al., 2011). This provides support for the marital discord model and also extends it by highlighting the potential for cross-partner effects and gender differences.

Self-Verification Theory

Katz and colleagues have integrated self-verification theory (Swann, 1983) with the marital discord model of depression (Beach et al., 1990) to explicate the reciprocal influences between relationship discord and depression. Self-verification theory posits that individuals tend to give preference to information about the self that matches their own self views. In romantic relationships, Katz and Beach (1997) documented that self-verifying feedback from partners may impact depressive symptoms. For example, negative self-verifying feedback may increase individuals' depression when individuals hold negative self views but may have little impact on marital quality as the feedback "fits" with the individual's self view. If, however, there is a mismatch in the individual's self view and the negative feedback, this may lead to conflict, relationship discord, and subsequent depression (for a review, see Katz, 2001).

Joiner and colleagues (e.g., Joiner, Alfano & Metalsky, 1993) have integrated Swann's verification theory with Coyne's (1976) model positing that depressed individuals seek reassurance from others in order to assuage feelings of low self-worth, but they also seek negative feedback confirming their negative self views. This conflicting behavior (seeking both positive and negative feedback) is posited to increase relationship dissatisfaction among partners of depressed individuals. Some work supports this model in the context of romantic relationships, especially for women (for a review see Starr & Davila, 2008).

Third Variable Models

There are several models proposing that the romantic relationship dysfunction–depression link may be explained by third variables, such as personality variables and interpersonal sensitivities, which contribute to the development of depression, relationship dysfunction, and the association between them (see Whisman, 2001a). One such theory expands beyond individual difference characteristics, proposing that power imbalances between men and women and stereotyped gender roles lead to wife-demand/husband-withdrawal interaction patterns, which in turn lead to both depression and relationship discord for women (Koerner, Prince & Jacobson, 1994). Koerner and colleagues suggest that this interaction pattern may render some women at greater risk for depression because it leads to self-silencing, reduced social reinforcement, and inadequate intimacy. In partial support of this, depressive symptoms were associated with wife-demand/husband-withdrawal interaction patterns and self-silencing for both husbands and wives, but self-silencing only mediated the link between marital dissatisfaction and depressive symptoms for wives (Uebelacker et al., 2003).

Attachment Theory and Developmental Psychopathology Perspectives

The developmental psychopathology perspective (Cicchetti, Rogosch, & Toth, 1994) posits that psychopathology is best understood from a life-span developmental approach that considers how effective negotiation and attainment of earlier developmental tasks influences individuals' capacities to effectively manage later tasks. Drawing on attachment theory (e.g., Bowlby, 1969), some developmental psychopathologists have proposed a transactional model to explain the development of depression (e.g., Cummings & Cicchetti, 1990). In this model, the early parent-child relationship leads to the development of internal working models about the self, others, and relationships, which then impacts interpersonal functioning and risk for depression (and other forms of psychopathology) throughout life. This model provides a framework for understanding the overlapping courses of depression and romantic dysfunction (e.g., Davila, 2001). It suggests that early difficulties (e.g., insecure parent-child relationships, deficits in interpersonal functioning, deficits in emotion regulation) may render individuals both unprepared to successfully negotiate adult romantic relationships as well as at greater risk for the development of depression. This notion has been one impetus for understanding the association between depression and romantic dysfunction at earlier developmental stages, particularly in adolescence.

Depression and Adolescent Romance

In this section, paralleling the adult literature, we describe research documenting the link between

romantic experiences (e.g., romantic attractions, activities, and relationships) and depression in adolescence. In addition, because adolescence is a developmental period in which sexual activities occur outside of the context of traditional romantic relationships, we also review the literature on romantic and sexual experiences in relation to depression.

Cross-Sectional Associations Between Romantic Experiences and Depressive Symptoms

Romantic experiences and depressive symptoms have been consistently linked in cross-sectional studies. For instance, adolescent girls who have more normative romantic activities (e.g., asking or being asked out on a date, flirting) and date more frequently exhibit greater self-reported depressive symptoms (e.g., Steinberg & Davila, 2008). However, research suggests that romantic involvement may not be uniformly associated with depressive symptoms. For example, it appears that some aspects of relationships may be associated with *greater* depressive symptoms, such as inhibiting self-expression to avoid conflict (Harper & Welsh, 2007), whereas other aspects, such as greater authenticity and intimacy, may be associated with *fewer* symptoms (Shulman, Walsh, Weisman, & Schelyer, 2009). Furthermore, research suggests that the link between romantic experiences and depressive symptoms may vary across individuals. For instance, among early adolescent girls, the association between engaging in normative romantic activities and depressive symptoms was stronger among girls with more emotionally unavailable parents (Steinberg & Davila, 2008). This suggests that romantic experiences may be particularly challenging for certain youth who may not have the interpersonal or emotional skills to negotiate these experiences.

Romantic Experiences Longitudinally Predict Depressive Symptoms

Evidence suggests that being in a romantic relationship predicts greater depressive symptoms during adolescence, particularly among early adolescents (Joyner & Udry, 2000). Certain adolescents may be especially vulnerable. For example, early adolescents who engage in corumination (i.e., excessive discussion of problems and heightened focus on negative emotions; Starr & Davila, 2009), as well as late adolescents who are higher on interpersonal sensitivity (Rizzo, Daley, & Gunderson, 2006) or who have a preoccupied relational style (Davila, Steinberg, Kachadourian, Cobb, & Fincham, 2004) experience greater increases in subsequent depressive symptoms. Furthermore, negative relationship events (e.g., intimate partner violence, breakups) and greater levels of romantic chronic stress (e.g., relationship instability, dissatisfaction with being single) predict increases in depressive symptoms and/or first onsets of MDD (Adam et al., 2011; Monroe et al., 1999; Shih, Eberhart, & Brennan, 2006). Together, these findings suggest that romantic experiences confer risk for depression, particularly among vulnerable youth who may use maladaptive coping strategies or may be more vulnerable to perceiving romantic stressors as distressing due to certain personality characteristics or interpersonal styles.

Depressive Symptoms Longitudinally Predict Romantic Experiences

Consistent with the bidirectional association between romantic experiences and depression, depression also predicts both the frequency and quality of romantic experiences. For instance, depressive symptoms predict more frequent relationship involvement (Davila, Stroud, et al., 2009), greater increases in romantic relationship conflict, and less growth in positive problem-solving skills (Vujeva & Furman, 2011). Also, among late adolescent girls, greater depressive symptoms predict greater rates of partners with cluster A (odd-eccentric) personality disorder symptoms, which in turn predict less perceived and partner-reported emotional support (Daley & Hammen, 2002). Thus depression may lead to problematic romantic experiences because adolescents lack the skills needed to effectively negotiate relationships or may select partners who fail to meet their needs, both of which may lead to further depression.

Cross-Sectional Associations Between Sexual Activities and Depressive Symptoms

In addition to romantic activities, engaging in sexual activities, either within or outside of the context of dating and relationships, has also been consistently linked with depressive symptoms. For instance, girls who are sexually active exhibit higher levels of depressive symptoms than those who are not sexually active; among those who are sexually active, depressive symptoms are highest among those who are active outside of dating relationships (e.g., Shulman et al., 2009). Additionally, having a greater number of sexual partners and not using contraception are associated with greater depression

(Kosunen, Kaltiala-Heino, Rimpela, & Laippala, 2003). Thus engaging in sexual activities, particularly risky ones, is linked with depression.

Sexual Experiences Longitudinally Predict Depressive Symptoms

There is mixed evidence regarding sexual experiences predicting depressive symptoms. For example, whereas findings suggest that girls from seventh to eleventh grade engaging in sexual intercourse are two to three times more likely to be depressed a year later compared with girls who abstain (Hallfors, Waller, Bauer, Ford & Halpern, 2005), other findings suggest that, for early adolescent girls, engagement in sexual intercourse and nonintercourse sexual activities does not predict an increase in depressive symptoms a year later (Davila, Stroud, et al., 2009). Given these mixed findings, more work is needed in this area.

Depressive Symptoms Longitudinally Predict Sexual Experiences

In contrast, there is fairly good evidence, particularly for early adolescents, that depressive symptoms predict future intercourse and nonintercourse sexual activities with a romantic partner (Davila, Stroud, et al., 2009), casual sex (Grello, Welsh, Harper, & Dickson, 2003), risky sexual behaviors (e.g., birth control non-use at last sex, having three or more sexual partners over the course of a year; Lehrer, Shrier, Gortmaker, & Buka, 2006), and an earlier age of first intercourse (e.g., Tubman, Windle, & Windle, 1996; Longmore, Manning, Giordano, & Rudolph, 2004). Importantly, early adolescents who engage in intercourse with romantic or casual sex partners show higher levels of depressive symptoms (and problem behaviors such as delinquency and violence) both before and after becoming sexually active compared with virgins (Grello et al., 2003), and those who engage in casual sex show higher levels of depressive symptoms than those who engage in intercourse with romantic partners only (Monahan & Lee, 2008). Together, these findings underscore the role of context in modifying the impact of sexual activity on risk of subsequent depressive symptoms. Furthermore, that differences in levels of depressive symptoms exist both prior to sexual activity and after supports the idea that depressive symptoms may be associated with early adolescent girls seeking out (or acquiescing to) certain types of sexual involvements, which may represent a maladaptive emotion regulation strategy and perpetuate depression.

To shed further light on the function of their association, moderators and specificity have also been examined. For example, the one-year longitudinal association between depressive symptoms and sexual intercourse is strongest among early adolescents who are highly avoidant of intimacy (Hershenberg & Davila, 2010) and whose parents report greater stress in the parent-adolescent relationship (Davila, Stroud, et al., 2009). This suggests that general comfort with being close to and depending upon others, as well as a more adaptive parent-adolescent relationship, may protect early adolescents from progressing to intercourse; conversely, sexual intercourse may represent an attempt to regulate emotions or seek support. Finally, recent work suggests that both depressive symptoms and externalizing symptoms predict increases in sexual activity over time among early adolescents (Starr et al., 2012). More work is needed to evaluate specificity.

In sum, a growing body of work supports bidirectional associations between adolescent romance and depression; romantic and sexual experiences are stressful and may lead to depression, particularly among vulnerable youth, and depressive symptoms may lead to increased frequency, as well as impaired quality, of romantic and sexual experiences.

Comorbid Depression–Romantic Dysfunction in Adolescents: Impact on School and Friends

Like the adult literature, research has not directly addressed this question in adolescence, but some findings speak to the impact of comorbid romantic experiences and depression on school experiences and friendships. For example, declines in school performance may play a role in the link between romantic involvement and subsequent depressive symptoms (Joyner & Urdy, 2000). Moreover, school involvement may facilitate sexual intercourse; depressed female adolescents were more likely to engage in sexual intercourse if they reported being more connected to school (Rink, Tricker, & Harvey, 2007). Finally, among depressed female adolescents, being closer to peers is associated with increased likelihood of engaging in sexual intercourse (Rink et al., 2007). Given these intriguing findings, examining the impact of the link between adolescence romance and depression on school and friendships merits attention.

Theory: Adolescent Romance and Depression

Adolescent romantic relationships have the potential to set the stage for adolescent emotional

thriving. However, as reviewed above, these experiences have also been linked with depression. In this section, we review theories explaining this link (see Davila, 2008).

Normative Trajectory Model

This theory states that adolescents engaging in off-time romantic activities, particularly precocious activities, will be at greater risk for depressive symptoms than adolescents engaging in on-time activities (Welsh, Grello, & Harper, 2003). Consistent with this, in early adolescence when involvement in a romantic relationship is not normative, those who are dating older romantic partners (Haydon & Halpern, 2010) or have first intercourse at an earlier age (e.g., Longmore et al., 2004; Spriggs & Halpern, 2008) show greater psychological distress than their nondating and sexually inactive peers. Importantly, however, romantic experiences and depressive symptoms are also associated with older adolescence (Davila et al., 2004; Joyner & Udry, 2000), suggesting that this theory may not fully account for the association.

Attention Impairment Model

Given evidence that romantic experiences are stressful and associated with increased preoccupation with negative emotional experiences (Larson, Clore, & Wood, 1999), Joyner and Udry (2000) proposed that this preoccupation will leave adolescents with fewer attentional resources to devote to learning, impairing their schoolwork and/or altering relationships with their parents. Supporting this, in a sample of adolescents, when poor school performance and family conflict were included in the model, the association between romantic experiences and change in depressive symptoms was reduced, showing that poor school performance and family conflict partially accounted for the association between romantic involvement and depressive symptoms. However, more work is needed to continue to evaluate this theory.

Stress and Coping Model

Romantic experiences can be a significant source of stress for adolescents including, for example, unreciprocated love, sexual behavior decision making, infidelity, and the beginning of a new relationship (e.g., Monroe et al., 1999; Welsh et al., 2003). The stress and coping model posits that stressors inherent in romantic experiences set the stage for adolescent depression and that these experiences will be particularly depressogenic among youth who lack sufficient coping skills. Consistent with this, among early adolescents who have had or are currently in romantic relationships, lower romantic competence (i.e., lower levels of interpersonal and emotional skills) is associated with greater dysphoria (Davila, Steinberg, et al., 2009). This supports the model, showing that adolescents who lack skills to effectively cope with and respond to stressors associated with romantic involvement are at risk for depression. Similarly, among girls who engage in greater levels of corumination, greater romantic experiences predict increases in depression (Starr & Davila, 2009), suggesting that maladaptive coping may render romantic experiences more depressogenic. Given that parents help adolescents regulate emotions, cope with the stress of romantic experiences, and provide a significant source of modeling (Davila, 2008), youth who do not receive sufficient coping resources from their parents may also be more vulnerable to depression. Supporting this, parental emotional unavailability and parent-adolescent attachment security moderate associations between romantic experiences and depressive symptoms (Steinberg & Davila, 2008).

Importantly, this model also allows for testing the opposite direction of effect. In other words, not only might lack of coping skills in the context of romantic experiences set the stage for depressive symptoms but depressive symptoms may lead adolescents to seek out romantic experiences as an emotion regulation strategy. As described, not only do consistent findings emerge with regard to depressive symptoms predicting sexual experiences (e.g., Lehrer et al., 2006), but comfort with intimacy also serves as a protective factor from engaging in sexual intercourse among early dysphoric adolescents (Hershenberg & Davila, 2010). These findings suggest that romantic and sexual activities may represent attempts to obtain support or cope with depression, particularly among those who are not comfortable being close to and depending upon others, which may inadvertently perpetuate dysphoria.

Individual Differences Model

The individual differences perspective posits that aspects of an adolescent's personality and/or interpersonal style may negatively impact his or her relationship experiences (or perception of those experiences), thereby strengthening the link between romantic experiences and depression among these vulnerable individuals. For example, greater rates of self-silencing in relationships predict

greater depressive symptoms, particularly for those engaging in frequent sexual intercourse (Little, Welsh, Darling, & Holmes, 2011). Further, the prospective link between romantic experiences and depressive symptoms is stronger among those with a preoccupied relational style (Davila et al., 2004) or who are higher on interpersonal sensitivity (Rizzo et al., 2006), suggesting that the link between romantic stressors and depression may be strongest among interpersonally vulnerable youth. Together, findings suggest that individual difference variables modify the romantic experiences–depression link.

Assessment and Intervention Strategies for Comorbid Depression–Romantic Dysfunction

In this section, we briefly review the empirical literature on couple therapy, compare individual versus couple interventions, and provide clinical guidelines for practitioners.

Couple Therapy for Co-occurring Depression and Relationship Distress

There is a growing body of research investigating the effectiveness of couple therapy for comorbid depression and relationship distress (e.g., Gupta, Coyne, & Beach, 2003; Beach, Dreifuss, Franklin, Kamen, & Gabriel, 2008 for reviews). Cognitive Behavioral Couple Therapy (CBCT; Beach et al., 1990; Epstein & Baucom, 2002) has accumulated the most support. Compared with individual cognitive therapy (CT), several studies show that CBCT (and slightly modified forms) is equally effective in reducing depressive symptoms posttreatment and at follow-ups but only CBCT improves marital satisfaction and other aspects of relationship functioning (e.g., Beach & O'Leary, 1992; Jacobson et al., 1991). Some work suggests that CBCT ameliorates depression by improving marital quality (e.g., Beach & O'Leary, 1992; Jacobson et al., 1991), but more work is needed to establish this as a mechanism of change.

Other couple approaches have also garnered support. For instance, a conjoint interpersonal approach (IPT-CM) (Weissman, Markowitz, & Klerman, 2000) has been found to be as effective as individual interpersonal therapy in reducing depressive symptoms and slightly more effective in enhancing the couple's relationship (Foley, Rounsaville, Weissman, Sholomskas, & Chevron, 1989). Also, emotionally focused couple therapy (Johnson, 2003) has received support, demonstrating equivalent posttreatment effects on depressive symptoms as compared with pharmacological treatment but a slight advantage during the follow-up period (Dessaulles et al., 2003). Furthermore, findings from a trial comparing systemic couple therapy, individual CT, and antidepressant medications in depressed individuals suggest that systemic couple therapy may also be effective (Leff et al., 2000). Finally, coping-oriented couple therapy, which combines strategies from behavioral marital therapy with dyadic coping strategies, was found to be as effective as well-established individual treatments in reducing depressive symptoms and demonstrated unique effects on partner criticism (for a review, see Sullivan & Davila, 2010). Thus there is emerging evidence for the efficacy of several approaches. However, further evaluation of their efficacy and effectiveness is needed (e.g., Gupta et al., 2003).

Individual Therapy Versus Couple Therapy

Converging evidence suggests that depressed individuals with comorbid relationship distress may benefit more from couple therapy than individual therapy. First, co-occurring relationship distress negatively impacts the outcome of individual therapy for depression (e.g., Whisman, 2001b). Second, for those in a relationship, comorbid depression-relationship distress appears to be the rule, rather than the exception, among individuals seeking treatment for depression (Atkins, Dimidjian, Bedics, & Christensen, 2009). Third, as reviewed above, both approaches appear to effectively reduce depression, but only couple therapy has a direct effect on marital quality (e.g., Barbato & D'Avanzo, 2008). When individual therapy improves marital quality, these effects appear to be mediated by changes in depressive symptoms (Whisman, 2001b), though alleviating depressive symptoms may not have a substantial impact on marital quality (Atkins et al., 2009). Finally, there is emerging evidence that conjoint treatment may be beneficial even for nondiscordant couples. For instance, a brief couple therapy for depression significantly reduced wives' depressive symptoms and positively impacted aspects of both partners' relationship functioning, regardless of level of relationship distress. This suggests that both partners may benefit from conjoint treatment (Cohen, O'Leary, & Foran, 2010).

Clinical Guidelines for Practitioners

Given that the CBCT approach has garnered the most support, our discussion of clinical guidelines will be based on this approach.

ASSESSMENT

Detailed assessment guidelines have been provided by others (e.g., Beach et al., 2008). Briefly, level of suicidality, depression, other forms of psychopathology, and various aspects of the relationship—including level of relationship discord, level of psychological and physical abuse, level of commitment, and the presence of infidelity—should be assessed using interview and self-report measures.

APPROPRIATENESS OF COUPLE THERAPY

Research suggests that couple treatment should be recommended for individuals experiencing comorbid relationship distress and depression (e.g., Barbato & D'Avanzo, 2008). Beach and colleagues (2008) suggest that CBCT is indicated when (1) there is low risk of suicide/suicidal behavior; (2) bipolar and delusional disorders are not present; (3) there is no evidence of intimate partner violence; (4) both partners are committed to improving the relationship; (5) neither partner plans for divorce and both are willing to be faithful; and (6) marital discord is present and appears to play a role in causing or maintaining the depression. Regarding the latter, there is also contradictory evidence suggesting that couple therapy may be indicated even at low levels of relationship distress (e.g., Cohen et al., 2010; also see the reviews by Kiecolt-Glaser & Newton, 2001; Whisman & Schonbrun, 2010).

Future Directions

How does comorbid romantic dysfunction-depression develop? The adult literature has almost exclusively studied couples within established relationships. However, examining factors that contribute to and modify the formation of relationships as well as romantic experiences outside of stable relationships further elucidate the development, timing, and mechanisms underlying the romantic dysfunction–depression association. This is perhaps best understood early in the course of individuals' romantic careers and prior to first onsets of MDD (e.g., Davila, 2001). Moreover, pursuing factors conferring risk for both romantic dysfunction and depression, such as skills deficits (Davila, 2008), family relationships (Davila, Stroud, et al., 2009) and emotion dysregulation (South et al., 2011) will elucidate how this comorbidity develops.

How does the course of depression affect comorbid romantic dysfunction and depression? Investigators need to attend more explicitly to the course of depression. For example, research needs to distinguish among factors related to the development, maintenance, recovery, relapse, and recurrence of depression; to elucidate factors that may be differentially related to first onsets versus recurrences; and to determine if course modifies treatment outcomes. Moreover, refining existing conceptual models to address the course of depression will serve to anchor the field and guide future research.

To what extent does current research generalize to different types of couples? To adult men and adolescent boys? Research has focused almost exclusively on heterosexual and/or married couples, Caucasians, depressed wives, and adolescent girls, leaving questions about whether research findings generalize to other types of couples, including cohabitating couples and same-sex couples, individuals from various ethnic/cultural backgrounds, depressed men, and adolescent boys. Given research documenting that the romantic dysfunction-depression association may vary according to the context of the relationship (e.g., Uebelacker & Whisman, 2006) as well as the recognition of the unique stressors associated with sexual minority status, it is imperative to examine associations with depression in the context of such relationships. Furthermore, although gender has received some attention in the adult literature, it is critical to continue to pursue gender differences, examine the efficacy of couple therapy for depressed men, explore the link between adolescent romance and depression in boys, and explicate theoretical models that account for gender differences in depression.

Is the link between romantic dysfunction and depression specific to depression? The answer is not yet clear; emerging research suggests that romantic dysfunction may be linked with a number of different forms of psychopathology in adolescents and adults, but associations with MDD and dysthymia may be particularly robust (e.g., Whisman, 1999). More work examining specificity is needed. Novel perspectives for psychopathology classification will also continue to advance the field (Brock & Lawrence, 2011; South et al., 2011). Further pursuit of these types of questions will deepen our understanding of comorbid relationship dysfunction and depression.

How can we advance research to deepen our understanding of the bi-directional link between romantic dysfunction and depression? The use of more sophisticated research methods, such as daily diary assessments, will increase our understanding of the bidirectional link, by illuminating day-to-day changes and the ways in which relationship events and depressed mood influence one another. In addition, long-term longitudinal studies that examine multiple factors in combination have the greatest

potential to illuminate the interplay among factors and the ways in which these interactions vary over time (e.g., Karney, 2001). The intriguing findings produced when multiple factors are examined using multiple methods and cross-partner effects are explored (e.g., Schudlich Du Rocher et al., 2011) highlight the contribution of this work.

How can we advance theory on the link between romantic dysfunction and depression? Dovetailing with the great contribution of research exploring the interplay of multiple factors, many researchers have called for the development of integrative theories. For example, Joiner (2001) merged six interpersonal and psychological theories of depression. Developing integrative theories such as this, which merge theoretical approaches and incorporate research on the nature of depression, will advance basic research and inform intervention research and development (e.g., Whisman, 2001b).

What types of couple therapy approaches demonstrate efficacy and effectiveness? As discussed, more work is needed to establish the efficacy of CBCT and other approaches of couple therapy in the treatment of comorbid depression and relationship dysfunction (e.g., Gupta et al., 2003) and to elucidate the mechanisms of change in these approaches (e.g., Barbato & D'Avanzo, 2008). In addition to further examining existing approaches, integrative behavioral couple therapy (IBCT) (Jacobson & Christensen, 1998) should be explored as a treatment for co-occurring depression and relationship distress. In a randomized controlled trial comparing traditional behavioral couple therapy (TBCT) with IBCT (which emphasizes both mutual acceptance and behavior change) in a highly maritally distressed sample, both treatments demonstrated similar levels of clinically significant improvement in marital satisfaction at five-year follow-up compared with pretreatment (Christensen, Baucom, Atkins, & Jean, 2010), and IBCT demonstrated greater maintenance of communication improvement over the two-year follow-up as compared with TBCT (Baucom, Sevier, Eldridge, Doss, & Christensen, 2011). These promising findings in a highly distressed sample compel an investigation of the efficacy of IBCT in the treatment of comorbid depression and intimate relationship dysfunction.

Furthermore, the generalizability of existing efficacy research remains a question for future work (e.g., Gupta et al., 2003). First, as discussed previously, existing research has focused on married, middle-aged heterosexual couples and depressed wives; thus, the extent to which this research generalizes to other types of couples remains a question for future work (e.g., Barbato & D'Avanzo, 2008; Beach & Gupta, 2003). Second, questions have been raised regarding the effectiveness of couple approaches for depression in community and primary care settings. As highlighted by Gupta and colleagues (2003), changes must be made to ensure the reach, availability, and acceptability of couple therapy in these settings. For example, challenges such as engaging both partners in therapy, accepting or maintaining the requirement of 12 to 20 conjoint sessions, and difficulty accessing providers trained in evidence-based treatments represent serious obstacles. Gupta and colleagues (2003) suggest developing alternate formats (e.g., psychoeducational workshops, unilateral therapy) and methods (e.g., telephone, internet) to increase the transportability of couple interventions to community and primary care settings. Evaluating the efficacy of couple approaches with different types of couples in community or primary care settings, with a focus on brief interventions (e.g., Cohen et al., 2010) as well as innovative methods and formats (e.g., Gupta et al., 2003) is a top priority for future work.

Conclusion

Our goal was to provide an overview of the literature on the comorbidity of romantic dysfunction and depression. As we hope is evident, research clearly suggests that romantic dysfunction can confer increased risk for depression. At the same time, depression can have deleterious consequences on intimate relationships, setting up a vicious cycle in which depression and romantic dysfunction reciprocally influence one another over time. Moreover, given that links between romantic experiences and depression begin early in adolescence, the co-occurrence of depression and romantic dysfunction may be lifelong and difficult to escape for those most vulnerable. However, the very components of romantic relationships that may be associated with depression, such as managing conflict, receiving and providing support and negotiating and balancing the needs of two people, also may lead to personal growth, joy, and thriving. As the field continues to advance in our understanding of who is most vulnerable and under what circumstances, our intervention and prevention efforts will become more effective in breaking the vicious cycle between romantic dysfunction and depression early in their overlapping courses, thereby promoting the development of intimate relationships that serve to protect people from depression rather than engender risk for it.

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CHAPTER

29 Family Relationships, Emotional Processes, and Adolescent Depression

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Abstract

This chapter reviews theory and research examining the co-occurrence of disrupted family functioning and adolescent depressive symptoms and disorders. It focuses on three key aspects of family functioning: family adversity, parent-child relationships, and parenting behavior. It concludes that research supports the presence of bidirectional associations between family functioning and adolescent depression. Furthermore, this chapter provides an integrative framework that conceptualizes emotional functioning as a key mechanism through which family relationships and adolescent depression mutually influence one another over time.

Key Words: disrupted family functioning, family adversity, parent-child relationships, parenting behavior, adolescent depression, emotional functioning

Introduction

In midadolescence, a sharp increase occurs in the diagnoses of depressive disorders (Kessler et al., 2005) and the occurrence of depressive symptoms (Angold, Erkanli, Silberg, Eaves, & Costello, 2002), particularly among girls. Multiple theories have been proposed to account for adolescents' heightened risk for depression (e.g., Hankin & Abramson, 2001; Hyde, Mezulis, & Abramson, 2008). Within these theories, stress and dysfunction in families are a common theme. Decades of empirical research have revealed that a broad range of disruptions in family functioning—including family adversity, poor quality family relationships, and maladaptive parenting behavior—frequently co-occur with adolescent depression (for a review, see Garber, 2005).

The developmental period of adolescence is a time of disequilibrium for many families (Steinberg, 2001). Parents and adolescents struggle to negotiate adolescents' heightened desire for autonomy (Steinberg, 2001), increasing involvement in activities outside the home (Larson, 2001), changes associated with pubertal maturation (Sagrestano, McCormick, Paikoff, & Holmbeck, 1999), and interest in sex and dating (Furman & Shaffer, 2003). Perhaps as a result of these challenges, negative affect in parent-child conflicts (Laursen, Coy, & Collins, 1998) and perceptions of family-related stress (Small, Eastman, & Cornelius, 1988) peak in midadolescence.

Researchers traditionally conceptualize disrupted family functioning as an etiological factor contributing to the onset of adolescent depression (Sander & McCarty, 2005), and longitudinal research supports this view. However, theoretical perspectives such as interpersonal theories of depression (Coyne, 1976; Gotlib & Hammen, 1992) and family systems theory (Cox, & Paley, 1997; Minuchin, 1988) suggest that symptoms of adolescent depression also may interfere with family functioning by disrupting interactions, placing strain on relationships, and undermining the emotional adjustment of other family members. In this way, disruptions in family functioning have the potential to be both a cause

and a consequence of adolescent depression. In this chapter, we discuss a variety of theoretical perspectives that propose links between family functioning and adolescent depression, and we explore the degree to which existing empirical findings support the proposed bidirectional associations.

This chapter also presents a framework for conceptualizing the integral role of emotional processes in explaining family precursors and consequences of adolescent depression (Figure 29.1). Depression is first and foremost an emotional disorder. Mood disruptions such as depressed mood, lack of positive affect, and irritability (in adolescence) are necessary for a diagnosis of depression (DSM-IV; American Psychiatric Association, 2000), and a growing body of research suggests that difficulty in processing and regulating emotional states is a central component of depression (for a review, see Aldao, Nolen-Hoeksema, & Schweizer, 2010). Understanding the role of emotion in depression is of particular import during adolescence, when many of the neural and cognitive systems that facilitate the regulation of emotion undergo critical periods of development (Lewis, Lamm, Segalowitz, Stieben, & Zelazo, 2006). A burgeoning literature on emotion socialization points to the central role that families play in shaping youths' emotional development (for a review, see Thompson & Meyer, 2007). Furthermore, much of the evidence linking family functioning and adolescent depression involves some aspect of emotions, such as family members' expressed emotions, parents' and adolescents' reactions to each others' emotions, and adolescents' regulation of emotion in the context of family interactions (e.g., Ehrmantrout, Allen, Leve, Davis, & Sheeber, 2011; Silk et al., 2009). Finally, aspects of emotional functioning such as the effective regulation of emotion and coping with stress may foster resilience to the negative effects of disrupted family relationships (Jaser et al., 2005; Silk, Shaw, Forbes, Lane, & Kovacs, 2006). Thus a central goal of this review is to explore the emotional processes through which family functioning and adolescent depression influence one another.

Theoretical Perspectives on Family Functioning and Adolescent Depression

Several theoretical perspectives provide frameworks for conceptualizing the complex processes underlying the co-occurrence of adolescent depression and impaired family functioning. Each highlights the unique role that family relationships play

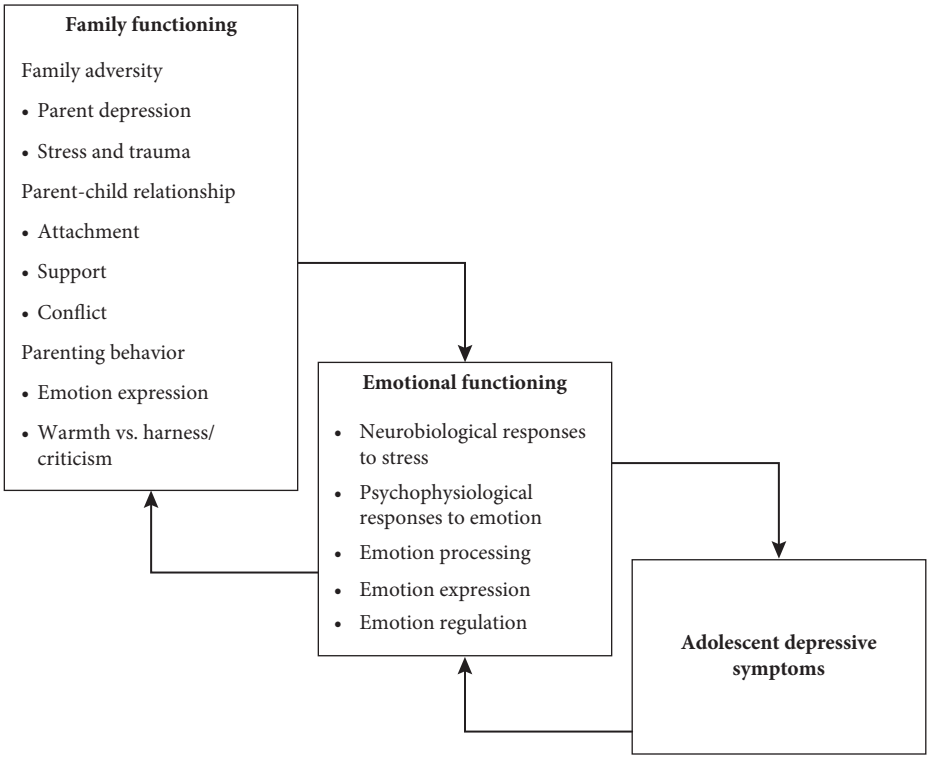

Figure 29.1 Transactional model of family relationships, emotional functioning, and adolescent depression.

in the etiology, maintenance, and consequences of adolescent depression, and each incorporates the notion of mutual influence among families and children over time.

Broadly, the field of developmental psychopathology provides a framework for considering bidirectional effects between family functioning and adolescent depression. A central goal in this field is to consider the complex processes that drive development over time. This goal is reflected in a growing focus on interactions and transactions between individual (e.g., child emotional functioning) and environmental (e.g., family environment, parenting style) factors as predictors of developmental pathways (Rutter & Sroufe, 2000). Another key tenet of developmental psychopathology suggests that investigations of typical development inform our understanding of atypical development and vice versa (Cicchetti & Toth, 2009). To this end, developmental psychopathology emphasizes dimensional approaches to studying mental health, such that empirical investigations of developmental processes may capture continuities and discontinuities in a wide span of functioning rather than focusing solely on discrete disorders (Rutter & Sroufe, 2000). Research supports the validity of dimensional approaches to measuring adolescent depression (Hankin, Fraley, Lahey, & Waldman, 2005) and suggests that the impact of subclinical symptoms on adolescents' well being is substantial (Lewinsohn, Solomon, Seeley, & Zeiss, 2000). Consequently this review considers empirical findings related to both depressive symptoms and diagnoses observed in community and clinical samples.

Family systems theory (Cox, & Paley, 1997; Minuchin, 1988) provides an additional framework for understanding how individual family members influence each other's development. Family systems theory proposes that a family is a "complex, integrated whole" (Minuchin, 1988, p. 8) comprising a series of interdependent subsystems (e.g., mother-father, mother-child, etc.) and that understanding the impact of each of these subsystems is essential to fully capture the role of the family in shaping development (Minuchin, 1988). Adjustment difficulties such as depression in one family member are expected to affect the well-being of all members of the system. Furthermore, reciprocity, or mutual influence between family members, is a central component of family systems theory. This perspective is consistent with the notion that family functioning both contributes to adolescent depression and is disrupted by it.

At a more specific level, interpersonal theories of depression provide a framework for considering transactional associations between family relationships and adolescent depression over time. Originally developed to help understand adult depression (Coyne, 1976; Joiner, 2002), interpersonal theories of depression suggest that characteristics of depressed individuals—such as mood changes, negative cognitive biases, and excessive reassurance seeking—disrupt relationships by eliciting negative responses from others (Coyne, 1976) and creating stress in the context of relationships (Rudolph et al., 2000). In this way, depression could have a toxic effect on the family system by adversely affecting other family members and creating stress and discord in the family environment. The disruptions in interpersonal functioning caused by a family member's depression are thought to maintain or even exacerbate the individual's depressive symptoms over time.

Rudolph, Flynn, and Abaied (2008) proposed a developmental interpersonal model of depression that seeks to explain the role that interpersonal functioning plays in the etiology and maintenance of depression in youth. This model proposes that early disruptions in family relationships, such as parent psychopathology or insecure attachment, contribute to a variety of social-behavioral deficits (e.g., difficulties with regulating emotions) in the developing child that serve to increase risk for depression both directly and indirectly through poor-quality or highly stressful relationships. Finally, the model proposes a feedback loop through which symptoms of depression maintain social-behavioral deficits and relationship disturbances, creating an ongoing cycle of dysfunction such that transactional effects between the adolescent and the family will contribute to the stability of youth depression over time.

Impaired Family Functioning as an Antecedent of Adolescent Depression

The majority of research examining family functioning and adolescent depression views adolescent depression as an outcome of familial factors. Behavior genetics research suggests that adolescent depression is moderately heritable (Rice, Harold, & Thapar, 2005) and supports the interactive contributions of genetic and environmental factors to adolescent depression (Silberg et al., 1999). A variety of aspects of family functioning have been implicated in predicting adolescent depression, including family adversity, parent-child relationships, and parenting behavior.

Family Adversity

PARENT DEPRESSION

A large body of research has examined risk for depression among offspring of parents with depressive symptoms or diagnoses. Depression in mothers (e.g., Hammen & Brennan, 2003; Kouros & Garber, 2010) and to some degree in fathers (e.g., Kane & Garber, 2004) is a robust predictor of depression in offspring. Prospective longitudinal studies reveal that exposure to maternal depression in childhood or early adolescence increases risk for onset of depression in adolescence (Garber & Cole, 2010; Halligan, Murray, Martins, & Cooper, 2007). Moreover, maternal depression is particularly likely to predict offspring depression in youths who experience early pubertal maturation (Rudolph & Troop-Gordon, 2010), suggesting that it is not just adolescent development per se but the context of this development that enhances sensitivity to maternal depression. Researchers have proposed that the intergenerational transmission of depression is due to a presumed genetic and neurobiological risk for depression transmitted from parent to child as well as children's exposure to parents' symptoms and functional impairments. Parenting behavior and family stress are two primary mechanisms through which parental depression heightens youths' risk for depression (Goodman & Tully, 2008).

According to interpersonal theories of depression, a parent's depressive symptoms will significantly disrupt their relationships with others, including their children. A large body of evidence suggests that a depressed parent's ability to provide consistent, supportive parenting is significantly impaired. Depressed parents appear to have particular difficulty with the emotional aspects of parenting; they exhibit a parenting style that is low in warmth, positive affect, and supportiveness and high in negative emotions such as criticism, hostility, and the induction of guilt. This emotionally negative parenting style has emerged consistently across youth reports (Garber & Cole, 2010), speech samples/interviews (Nelson, Hammen, Brennan, & Ullman, 2003; Silk et al., 2009), and observations of depressed mothers' interactions with their offspring (for a meta-analysis see Lovejoy, Graczyk, O'Hare, & Neuman, 2000). Longitudinal research suggests youths' exposure to negative parenting partly explains the prospective relation between parent and adolescent depression (Garber & Cole, 2010; Nelson et al., 2003).

Interpersonal theories of depression also suggest that having a depressed parent will create a variety of stressors in the family environment; similarly, according to family systems theory, stress or other disruptions in parents' functioning will adversely affect the depressed parent's offspring. Youths with a depressed parent are in fact more likely to be exposed to concurrent stressful life events (Hammen, Brennan, & Shih, 2004) than children of healthy parents, and longitudinal research suggests that stressful life events mediate the prospective association between parent and adolescent depression (e.g., Garber & Cole, 2010). Jones, Beach, and Forehand (2001) found that mothers' depressive symptoms predicted increased stress in their relationships with their adolescent offspring, which partially accounted for the prospective link between mothers' and adolescents' depressive symptoms. Importantly, effective coping with family stress mitigates the adverse effects of parental depression on youth adjustment (Jaser et al., 2005; 2008). Thus considerable evidence supports disrupted parenting and stress exposure as explanatory mechanisms through which parental depression contributes to adolescent depression.

Guided by such findings, Compas and colleagues (2010) developed a two-pronged intervention designed to improve parenting skills and youth coping with family stress in families with a depressed parent; the intervention significantly reduced symptoms of psychopathology in youth, and these effects were mediated in part by improvements in parenting skills and children's coping with family stress (Compas et al., 2010). The effectiveness of this intervention provides further evidence that negative parenting and family stress are causal mediators of the intergenerational transmission of depression. The success of the child coping portion of the intervention also supports the idea that the ability to self-regulate in the face of stress promotes resilience to the adverse effects of disrupted family functioning. Furthermore, these results provide a promising indication that the negative cycle of depression in families can be interrupted.

STRESS AND TRAUMA IN THE FAMILY

In addition to parent depression, longitudinal and retrospective research suggests that exposure to early stress and trauma—such as parental loss, abandonment, maltreatment, or divorce—is associated with heightened risk for depression later in development (for a review, see Goodman, 2002). Building on these findings, some studies have found evidence supporting stress sensitization, a process whereby early adversity heightens reactivity to recent stressors such that youths who have experienced early

adversity in the family have a lower threshold for developing depression in response to recent stress than those who have not had such experiences (e.g., Harkness, Bruce, & Lumley, 2006). Of interest, some research suggests that this process of stress sensitization is particularly salient in girls who have progressed through puberty, providing some insight into the heightened risk for depression in adolescent girls (Rudolph & Flynn, 2007).

Research seeking to explain the high rates of psychopathology among youths living in poverty has revealed that economic strain on the family is a particularly potent predictor of depression and other mental health problems (e.g., Santiago, Wadsworth, & Stump, 2011). The mechanisms through which family economic strain affects adolescent adjustment are similar to those for parent psychopathology. Research conducted by Conger and Conger (2002) and Gutman, McLoyd, and Tokoyawa (2005) suggests that economic strain affects children's development indirectly by fostering interpersonal conflict and emotional distress in parents and disrupting parent-child relationships. Others have found that economic strain increases risk for depression by creating stress experienced directly by youth; however, youth who engage in adaptive coping behaviors in the face of economic strain are less likely to develop symptoms (Wadsworth & Berger, 2006; Wadsworth, Raviv, Compas, & Connor-Smith, 2005).

EMOTIONAL PROCESSES IN FAMILY ADVERSITY

A growing body of evidence suggests that early family adversity contributes to depression by undermining the development of adaptive emotional functioning and heightening stress reactivity. Early adversity in the form of parent depression, maltreatment, or other stressors may increase youths' reactivity to later stressful events by altering the development of neurobiological and physiological systems involved in stress reactivity, emotion regulation, and emotion processing (for a review, see Gunnar, 2010). Consistent with a developmental psychopathology perspective, early exposure to adverse environments could initially direct children along a path to maladaptation; children's ability to divert from this problematic pathway could be constrained by the biological changes associated with adversity, a process known as entraining (Boyce & Ellis, 2005). For example, exposure to maternal depression or trauma/abuse early in development is associated with heightened reactivity of the hypothalamic-pituitary-adrenal (HPA) axis later in development (e.g., Essex et al., 2002; Kertes, Gunnar, Madsen, & Long, 2008) and with disrupted neural processing of emotional stimuli, as indexed by event-related potentials (ERPs) (e.g., Cicchetti & Curtis, 2005; Kujawa, Hajcak, Torpey, Kim, & Klein, 2012). Importantly, both HPA functioning and neural processing of emotions are implicated in adolescent depression (for respective reviews see Brooks-Gunn, Auth, Peterson, & Compas, 2001; Forbes & Dahl, 2005). Given that research supports early parental psychopathology and adversity as temporal precursors to neurobiological and psychophysiological reactivity as well as adolescent depression, disruption in these systems is a plausible mechanism through which early adversity instills long-term risk for depression in youths. However, research must explicitly test the proposed mediational pathways in adolescent populations.

Parent socialization of emotion and youths' cognitive and behavioral emotion regulation may represent additional mechanisms through which family adversity increases risk for depression. Research suggests that offspring of depressed parents (e.g., Feng et al., 2008; Silk et al., 2006) and offspring of maltreating parents (e.g., Kim & Cicchetti, 2010) are less skilled at regulating emotions than offspring of healthy, nonabusive parents. Researchers have begun to examine whether maladaptive parent socialization of emotion underlies emotion regulation difficulties among youths exposed to family adversity. As discussed above, depressed parents frequently express intense, irritable, and hostile emotions, many of which are directed at the child, which may interfere with the child's development of effective strategies to regulate emotion (Eisenberg, Cumberland, & Spinrad, 1998). Depressed or abusive parents also show disrupted patterns of responding to children's emotions. One study found that compared with nondepressed parents, depressed parents were less responsive to children's emotions (Shaw et al., 2006). Another study found that maternal depressive symptoms predicted lower levels of maternal encouragement to think positively about stress and higher levels of maternal encouragement to avoid stress or negative emotions (Monti, Rudolph, & Abaied, 2014). Depressed parents are also more likely than nondepressed parents to punish, amplify, or disengage from children's negative emotional displays, which in turn predicts children's internalizing symptoms (Silk et al., 2011). Similarly, abusive or neglectful parents are less likely to discuss emotions with their children (Edwards, Shipman, & Brown,

2005; Shipman & Zeman, 1999) and have more difficulty coping with and supporting children's negative emotions than nonabusive parents; these socialization behaviors are in turn associated with less effective regulation of emotions and heightened internalizing symptoms in children (Shipman et al., 2007). Furthermore, children's regulation of emotion has been found to mediate the prospective association between maltreatment and internalizing symptoms (Alink, Cicchetti, Kim, & Rogosch, 2009; Maughan & Cicchetti, 2002). More research is needed to directly examine whether both parental emotional socialization and offspring emotional regulation mediate the association between early family adversity and depression in adolescence.

In sum, considerable evidence supports the idea that family adversity increases adolescents' risk for developing subsequent depression. An emotionally negative parenting style is a key mechanism through which family adversity affects adolescents' development. The processing and regulation of emotion as well as reactivity to and coping with stress are also central to the process whereby parental psychopathology and adversity contribute to adolescent depression.

Parent-Child Relationships

Beyond the broader family context, theory and research have considered the role of problematic parent-child relationships as risk factors for adolescent depression. Here we focus on two aspects of the parent-child relationship that have received widespread attention: insecure attachment and low perceived support/high conflict.

ATTACHMENT

Attachment theory (Bowlby, 1969) proposes that in the first years of life children develop lasting emotional bonds with caregivers or attachment figures. According to attachment theory, the nature of interactions with caregivers, especially how caregivers respond to the child's distress, shape the developing child's implicit beliefs about relationships with others (i.e., as supportive, consistent, and available versus unsupportive, unreliable, and distant) and the self (as worthy versus unworthy of love and care). These beliefs, or attachment representations, endure throughout development, such that attachment to caregivers forms a foundation for future relationships (Bowlby, 1969). Furthermore, given that attachments are formed in the context of children seeking comfort when they are distressed, researchers have proposed that attachment representations shape how individuals respond to stress and regulate emotions (Shaver & Mikulincer, 2007).

Bowlby (1969) predicted that insecure attachment would place individuals at risk for developing social and emotional difficulties later in development; others have argued that individuals with insecure attachments are particularly vulnerable to depression (Morely & Moran, 2011). Although most of the evidence linking insecure attachment and depressive symptoms in adolescence is cross-sectional and thus does not speak to direction of effect (e.g., Abela et al., 2005), a small number of longitudinal studies reveal that insecure attachment predicts subsequent depressive symptoms in adolescence (e.g., Allen, Porter, McFarland, McElhaney, & Marsh, 2007; Lee & Hankin, 2009).

Why might insecure attachment be a precursor to depression? Morely and Moran (2011) argue that early insecure attachment fosters feelings of low self-worth (a common symptom of depression) and beliefs about the self as incapable of independently managing stress and challenge; consequently insecure individuals tend to exhibit helpless behavior in the face of stress, which increases their vulnerability to depression. Others posit that implicit beliefs that others cannot be relied upon for support and nurturance in times of stress contribute to the maladaptive patterns of responses to stress and emotion regulation, such as rumination or avoidance, typically observed among adults with insecure attachment representations (Shaver & Mikulincer, 2007). Similarly, interpersonal theories of depression propose that depressed individuals are often dissatisfied with the support they receive from other people (Coyne, 1976), which is strikingly consistent with an insecure attachment representation of others as unavailable or unsupportive in times of stress.

Emotional processes also likely explain the link between insecure attachment and depression. Several studies suggest that adolescents with insecure attachment representations have difficulty regulating emotions. Seiffge-Krenke (2006) found that insecure attachment was linked to heightened perceptions of parent-related stress and a tendency to avoid interpersonal stressors throughout adolescence and early adulthood. Similarly, adolescents with insecure attachment representations have been shown to be less skilled at regulating emotion in the context of problem-solving interactions with parents (Kobak, Cole, Ferenz-Gillis, Fleming, & Gamble, 1993) and a close friend (Zimmerman, Maier, Winter, & Grossmann, 2001) as compared

with secure adolescents. Importantly, cross-sectional studies have found that negative attributions regarding relationship stress (Margolese, Markiewicz, & Doyle, 2005), rumination (Ruijten, Roelofs, & Rood, 2011), and a high need for approval from others for self-worth (Shirk, Gudmundsen, & Burwell, 2005) mediated the concurrent association between insecure attachment and depressive symptoms. Longitudinal replication of these patterns is needed to draw stronger conclusions regarding direction of effect, but these studies provide preliminary evidence that maladaptive responses to stress and the regulation of emotion could be mechanisms whereby insecure attachment sets the stage for depression later in development.

SUPPORT AND CONFLICT

Other research has examined the contributions of more specific aspects of the parent-adolescent relationship, such as support and conflict, to adolescent depression. Considerable longitudinal evidence suggests that adolescents' perceptions of parents as unsupportive or untrustworthy predict subsequent depressive symptoms (e.g., Allen et al., 2006; Branje, Hale, Frijns, & Meeus, 2010). One study found that youths who perceive more parental support showed lower levels of depressive symptoms and a steeper decline in depressive symptoms over time compared with adolescents who perceived less parent support (Needham, 2007). Similarly, a close, trusting parent-adolescent relationship has been found to buffer adolescents from developing depressive symptoms subsequent to stressful life events (Ge, Natsuaki, Neiderhiser, & Reiss, 2009). Some evidence also suggests that perceived support from parents is more strongly linked to depression than support from peers. Stice, Ragan, and Randall (2004) found that perceived support from parents predicted subsequent (increases in) depressive symptoms, whereas perceived support from peers did not. Another study found that adolescents who relied more on friends than family for support were more likely to experience the onset of a depressive episode, suggesting that adolescents who are reluctant to rely on parents for support are at heightened risk for depression (McFarlane, Bellissimo, Norman, & Lange, 1994). Finally, parent-adolescent conflict—as assessed by observations of parent-adolescent interactions, adolescent reports, and parent reports—predicts subsequent depression in adolescents (Lewinsohn et al., 1994; Sheeber, Hops, Alpert, Davis, & Andrews, 1997). One study found this association to be strongest among youths with a genetic risk for depression (Rice, Harold, Shelton, & Thapar, 2006).

Research has not yet examined whether or how emotional processes mediate the link between support/conflict and adolescent depression. The perception of low levels of support and high levels of conflict in parent-child relationships could undermine adolescents' inclination to seek emotional support, thereby leaving them vulnerable to depression. Moreover, high levels of conflict may be accompanied by frequent expressions of negative emotions between family members, which could undermine adolescents' emotional adjustment. However, additional research is needed to establish these proposed pathways.

In sum, ample evidence suggests that the quality of the parent-child relationship predicts depression in adolescence. Specifically, a secure, supportive, trusting, low-conflict relationship between parents and adolescents appears to protect adolescents from developing later depression. In contrast, a parent-child relationship that is insecure, unsupportive, or high in conflict contributes to heightened risk for subsequent depression.

Parenting Behavior

Much of the work investigating links between parenting behavior and adolescent depression has focused on offspring of depressed parents; yet parents with no current or past depression may also contribute to adolescents' risk for depression through their parenting behavior. Cross-sectional studies suggest that exposure to hostile, negative, and psychologically controlling parenting behaviors are consistently linked with adolescent depression (for a review, see Sheeber, Hops, & Davis, 2001). Comparatively fewer studies have examined whether parenting predicts future depression in adolescents (in families without a depressed parent), but longitudinal research does suggest that parenting related to emotions and stress contributes to the development of adolescent depression.

Multiple studies support the idea that an emotionally negative parenting style increases adolescents' risk of future depression. Ge, Best, Conger, and Simons (1996) found that low parental warmth and high parental hostility in midadolescence predicted depressive symptoms in late adolescence in a sample of lower- to -middle-class rural families. Sagrestano, Paikoff, Holmbeck, and Fendrich (2003) observed similar prospective effects over a one-year period in a sample of inner-city African American families. High levels of parental criticism

also predict the onset (Silk et al., 2009) and maintenance (McCleary & Sanford, 2002) of depression in adolescence. Furthermore, a parenting style high in psychological control (e.g., inducing guilt, withholding affection), predicts heightened depressive symptoms over time (Soenens et al., 2008).

The emotional dynamics of parent-adolescent interactions also play a role in predicting subsequent depression. One study found that coercive family interactions in early childhood, in which parents and youth reciprocate aversive behaviors directed toward each other during conflicts, predicted depression in adolescent girls (Compton, Snyder, Schrepferman, Bank, & Shortt, 2003). Schwartz et al. (2011) found that adolescents were at heightened risk for subsequent depression if mothers responded to their aggression (i.e., anger, hostility, disruptive behavior) with depressive behaviors (i.e., complaints, self-derision, sadness) and to their depressive behaviors with low levels of aggression. These effects become more complex in the context of triadic interactions between mothers, fathers, and adolescents. Davis, Sheeber, Hops, and Tildesley (2000) found that girls who attempted to comfort their mothers when their fathers directed depressive behaviors toward their mothers were most likely to be depressed one year later; boys, however, were most likely to show subsequent depression if they displayed aggressive behavior toward their mothers when mothers directed depressive behaviors toward fathers. Although additional research is needed to replicate these complex findings, these studies further support the central role of emotions in the link between parenting behavior and adolescent depression.

Parents' explicit socialization of emotions and coping with stress may also contribute to adolescents' risk for future depression; however, most of the research examining this link in adolescents is cross-sectional. For example, adolescents show higher concurrent depressive symptoms if mothers discourage or invalidate their positive emotions (Yap, Allen, & Ladouceur, 2008) and if mothers are low in acceptance and expression of their own emotions (Katz & Hunter, 2007). One longitudinal study found that youths whose mothers primarily encouraged avoidance of stress and emotions were at heightened risk for subsequent depression in early adolescence, particularly in the context of high interpersonal stress (Abaied & Rudolph, 2010). Given the central role of emotional socialization observed in the literature on the intergenerational transmission of depression, more longitudinal research is needed to examine these processes in families without a history of depression.

In sum, research suggests that an emotionally negative parenting style characterized by hostility, criticism, and discouragement of positive affect contributes to the development of depression in adolescence. This pattern has been observed at both macro- (i.e., parenting style) and microlevels (i.e., moment-to-moment emotional contingencies in parent-adolescent interactions).

Impaired Family Functioning as a Consequence of Adolescent Depression

Although most research investigating depression within families examines the contribution of family disruption to subsequent adolescent depression, some research considers the reciprocal effect of adolescent depression on the family. Depressive symptoms and associated impairment can disrupt the family system in a variety of ways, such as by creating family stress, placing strain on the parent-adolescent relationship, and eliciting negative parenting. Compared with the familial antecedents of adolescent depression, much less is known regarding the emotional processes involved in the consequences of adolescent depression. Thus, we present tentative hypotheses regarding the role of emotional functioning in areas where relevant empirical findings are not available.

Family Stress

Depressed youth have been shown to contribute to stressful events in their lives (e.g., Cole, Nolen-Hoeksema, Girgus, & Paul, 2006; Davila, Hammen, Burge, Paley, & Daley, 1995), a process known as stress generation (Hammen, 2006). Consistent with interpersonal theories of depression, studies that differentiate between types of stress suggest that depression is comparatively more likely to lead to interpersonal than noninterpersonal stressors (Daley et al., 1997; Rudolph et al., 2000). One study found that the generation of interpersonal stressors contributed to the maintenance of depression over time in early adolescent girls but not boys (Rudolph, Flynn, Abaied, Groot, & Thompson, 2009), providing direct support for a reciprocal-influence model. These studies combine stressors across multiple interpersonal relationships (e.g., family, peers, romantic partners) such that the unique contribution of depression to family-related stress is unclear. However, these studies do provide evidence that adolescent depression can create stress in the context of relationships, as predicted

by interpersonal theories of depression (Gotlib & Hammen, 1992).

Adolescent depression has the potential to create stressful events and emotional distress for other family members as well. Hinshaw (2005) argues that there is a stigma associated with having a child with a mental illness, which may create stress and discomfort for family members or even prevent them from seeking services for their child. Consistent with this view, parents of youths with internalizing problems (including depression) report feeling burdened by their child's mental illness in a variety of ways, such as strain in the marital relationship, disruptions in personal and family activities, fatigue, and negative emotions such as worry (e.g., Angold et al., 1998; Meltzer, Ford, Goodman, & Vostanis, 2011). The parental burden of internalizing problems appears to be stronger in socioeconomically disadvantaged families (Meltzer et al., 2011) but lower compared with externalizing problems, perhaps because internalizing problems are often difficult to observe directly (Angold et al., 1998; Meltzer et al., 2011).

The stigma and burden associated with having a depressed adolescent can also create or amplify stress, negative emotions, and psychopathology in parents. For example, parents may experience self-blame, guilt, or low self-worth as a result of their adolescent's depression, or the adolescent's symptoms may overtax parents' resources for sensitive, supportive parenting and create stressful events in the family. Guilt, low self-worth, or heightened stress can in turn amplify parents' risk for psychopathology such as depression. One longitudinal study found that adolescents' psychopathology at age 15 predicted higher maternal depression over the course of the following five years; furthermore, this effect was partly explained by mothers' reports of heightened stress in their relationship with their adolescent (Raposa, Hammen, & Brennan, 2011). Although additional longitudinal research is needed to examine the unique effects of adolescent depression, this study provides preliminary evidence that adolescent depression might lead to future family stress and parent psychopathology, particularly mood disorders such as depression. The broader stress literature supports the hypothesis that stressful conditions (e.g., disruption in family life, stigma) will undermine family members' ability to effectively regulate negative emotions (for a review see Sapolsky, 2007), but this has not been examined directly in families of depressed adolescents.

In sum, a limited amount of evidence supports the idea that adolescent depression creates subsequent stressful conditions, emotional distress, and impairment in other family members as predicted by interpersonal theories of depression and family systems theory. However, more research is needed to characterize the precise types of stress and ensuing emotional processes that emerge in the families of depressed adolescents.

Family Relationships

The symptoms and impairment associated with depression may place strain on the parent-adolescent relationship. Depression is associated with a number of cognitive biases, such as negative views of the self and others. Although such biases often exist before the onset of depression, constituting vulnerability (Carter & Garber, 2011), research suggests that cognitive biases also increase after the onset of depression (Garber, Keily, & Martin, 2002). Depressed adolescents' cognitive biases can create negative perceptions of their family relationships. Interpersonal theories of depression posit that depressed individuals are biased to perceive the support of others as inadequate (Coyne, 1976) and may attempt to compensate by persistently seeking confirmation of self-worth, love, and acceptance, a phenomenon known as excessive reassurance seeking (Joiner, Metalsky, Katz, & Beach, 1999). Excessive reassurance seeking is thought to place strain on relationships and ultimately undermine the quality of support that others provide (Coyne, 1976; Joiner et al., 1999). In this way, depressed adolescents may elicit discomfort in significant others and rejection by them, creating a cycle of depression and interpersonal disturbances.

Some research supports the idea that depression is associated with increasingly negative perceptions of family relationships. Depressive symptoms predict subsequent lower perceived relationship quality with parents (Allen et al., 2006; Branje et al., 2010) and lower perceived support from parents (Needham, 2007), although one study found this link for girls but not boys (Slavin & Rainer, 1990). Shirk, Van Horn, and Leber (1997) found that depressed preadolescents viewed maternal figures in videotaped parent-adolescent interactions as less supportive and less helpful than did nondepressed preadolescents regardless of the level of observer-rated supportiveness, suggesting that this bias may not be specific to one's own parents but also extend to new interpersonal contexts. Contrary to these findings, two studies did not observe declines in perceived parent support following adolescent depression (Sheeber et al., 1997; Stice et al., 2004). Very little research

has examined the effects of adolescent depression on family conflict. Sheeber et al. (1997) found that conflict remained stable and high among depressed adolescents but did not increase over time as a function of depression. Given that low-quality family relationships often precede adolescent depression, adolescents' depressive symptoms may serve to reinforce disrupted relationships in some families, such that family functioning remains consistently poor after the onset of adolescent depression.

Long-term longitudinal studies reveal that depressed adolescents are likely to experience disruptions in their adult relationships. Specifically, young adults who were depressed as adolescents experience low-quality family relationships and small social networks (Lewinsohn, Rohde, Seeley, Klein, & Gotlib, 2003; Weissman et al., 1999) as well as insecure romantic attachments in women and an antagonistic interpersonal style in men (Gjerde & Westenberg, 1998). In this way, the interpersonal consequences of adolescent depression are potentially long-lasting. The cognitive biases and impairments associated with depression can perpetuate interpersonal difficulties across the transition to adulthood. Indeed, Davila et al. (1995) found that difficulties in interpersonal problem solving and subsequent interpersonal stress partly accounted for the one-year stability of depressive symptoms in young adults; those with a history of depression may be ill equipped to effectively manage interpersonal stressors.

Research has yet to examine the emotional processes through which adolescent depression undermines subsequent family relationship quality. It is possible that depressed adolescents who perceive parental support as inadequate are more likely to express negative emotions such as anger, frustration, or sadness toward parents. Negative interactions with depressed adolescents, particularly if parents' attempts at support are rejected, can also elicit negative emotional displays from parents directed toward adolescents. In this way, declining parent-adolescent relationship quality may be a catalyst for increasing negative emotional dynamics in parent-adolescent interactions.

Parenting Behavior

Children with adjustment difficulties may pose unique challenges that constrain the cognitive, emotional, and interpersonal resources available for warm, supportive, and consistent parenting (Collins, Maccoby, Steinberg, Hetherington, & Bornstein, 2000). Much of the research examining children's elicitation of negative parenting behavior has focused on conduct problems (e.g., Anderson, Lytton, & Romney, 1986), yet adolescent depressive symptoms such as sadness, anhedonia, irritability, low self-worth, or disturbed appetite and sleep also have the potential to foster stress and negative reactions from parents. However, very little research has examined this question directly; one study found that depressed youth report more hostile, harsh, and inconsistent parenting over time compared with nondepressed youth (Kim, Conger, Elder, & Lorenz, 2003).

Symptoms of depression may undermine supportive parenting behavior by interfering with adolescents' ability to effectively regulate emotions in the context of interactions with their parents. Research suggests that depressed children and adolescents have difficulty accurately interpreting affective stimuli (Mendlewicz, Linkowski, Bazelmans, & Philippot, 2005; van Beek & Dubas, 2008). Observations of parent-child interactions have revealed that depressed youth show less problem-solving behavior and more dysphoric affect than nondepressed adolescents (Sanders, Dadds, Johnston, & Cash, 1992; Sheeber & Sorenson, 1998). Sheeber, Allen, Davis, and Sorenson (2000) found that in the context of a parent-child problem-solving task, depressed adolescents had more difficulty recovering from prolonged bouts of depressive behavior such as self-criticism, whining, or dysphoria than did nondepressed adolescents. Furthermore, depressed adolescents appear to misinterpret parents' affect compared with the views of independent observers (Ehrmantrout et al., 2011). Adolescents' symptoms or difficulties in regulating their emotions also may have direct effects on parents; for example, mothers of depressed adolescents are more likely to show contingent facilitative reactions to adolescents' depressive behavior in parent-child interactions than mothers of nondepressed adolescents (Sheeber & Sorenson, 1998). Furthermore, mothers' contingent facilitative reactions (i.e., positive affect, approval) to adolescents' depressive behavior can contribute to adolescents' difficulties in regulating their emotions. Sheeber et al. (2000) found that adolescents were more likely to reciprocate maternal negative affect and exhibit prolonged depressive behavior if mothers showed facilitative reactions to their depressive behavior, such that mothers appeared to be reinforcing their adolescents' depressive symptoms. In this way, disrupted emotional functioning may represent a pathway through which adolescent depression undermines constructive parenting.

Implications for Assessment and Treatment

Adolescents seeking treatment for depression are likely to benefit from clinical approaches that focus on emotional processes in the family. Assessments of parental emotional socialization (including modeling and reactions to others' emotions), the emotional expressiveness of family members, and patterns of family communication about emotion would provide critical insight into potentially fruitful targets for intervention. These assessments may include interviews or questionnaires completed by parents and adolescents as well as observations of family interactions.

Interventions seeking to improve family functioning in families of depressed adolescents or parents should consider aiming to build emotional resources and adaptive patterns of emotional interaction. Parenting components of interventions could include education about how depression (in parents or adolescents) has the potential to create interpersonal stress and influence perceptions of relationships. Parents of depressed adolescents would benefit from training in how to adaptively model and express their own emotions as well as how to adaptively react to adolescents' emotions. Exercises in a family context could include guided practice expressing emotions to family members and reacting supportively to family members' expression of emotions. By addressing these family-level emotional processes as well as adolescents' symptoms, more favorable treatment outcomes may ensue, which may help to prevent the maintenance or recurrence of depression.

Conclusion

In sum, research supports the idea that disruptions in family functioning, including family adversity, poor quality parent-adolescent relationships, and maladaptive parenting behavior, are both antecedents and consequences of adolescent depression. Furthermore, emotional processes can be construed as key mediators of reciprocal linkages between family disruption and adolescent depression. These patterns are consistent with the idea that both interpersonal and emotional processes are fundamental components of depression.

Future Directions

We propose four key directions for future research. First, considerably more evidence exists supporting family functioning as an antecedent than a consequence of adolescent depression, yet it is unclear to what degree this is an actual phenomenon (i.e., familial factors are more likely to predict depression than to be affected by depression) or simply the result of a disproportionate number of investigations examining this directional pathway. Longitudinal studies focusing on the consequences of adolescent depression for various aspects of the family system are thus a crucial next step for this area of research.

Second, investigations are needed that directly examine emotional processes as mediators of the association between family functioning and adolescent depression. Some mediational pathways have support in younger children yet require replication in adolescents (e.g., the regulation of emotion mediating links between maternal depression and youth adjustment), whereas others have not been addressed in any population (e.g., physiological emotional reactivity mediating links between early family adversity and youth depression). In addition, emotional processes involved in some aspects of family functioning are less understood than others; there is a particular need for research examining the emotional correlates of parent support and parent-adolescent conflict.

Third, the majority of research reviewed in this chapter examines family functioning but does not assess other interpersonal relationships. Direct comparisons of the role of family functioning relative to other relationships such as peers or romantic partners are needed to determine whether the bidirectional links between family functioning and adolescent depression are unique to the family domain or simply indicative of broader interpersonal processes. Such comparisons are of particular import in adolescence, when youths' involvement and emotional investment in peer and romantic relationships increase (Furman & Shaffer, 2003). For example, does family stress predict depression above and beyond the effects of peer stress? Alternatively, do adolescents' depressive symptoms have similar or disparate effects on the quality of relationships with parents versus peers or romantic partners? Answers to these questions will elucidate the relative importance and broader context of family functioning as it relates to adolescent depression.

Finally, although individual studies support most of the unique pathways proposed in our integrated model (Figure 29.1), very few studies have examined reciprocal effects between family functioning and adolescent depression. Thus there is an urgent need for longitudinal research that incorporates multiple assessments of both family and adolescent functioning, such that transactional, prospective effects can

be tested. Incorporation of emotion-related variables (e.g., the expression and regulation of emotion) into longitudinal study designs would provide a direct test of the mediational pathways proposed in our integrative model.

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CHAPTER

30 Perinatal Depression

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Abstract

Depression is a common problem among pregnant and postpartum women, with rates comparable to or greater than those among women of childbearing age who are not pregnant or postpartum. Perinatal depression is associated with a wide range of unique assessment and treatment complexities, risk factors, and consequences for women and offspring. In this chapter, we review current research on the prevalence of perinatal depression, etiology, risk factors, and consequences, and we discuss assessment strategies and interventions. Limitations to current research and future research directions are noted. We conclude with guidelines for practitioners for assessing and treating depression during the perinatal period.

Key Words: depression, perinatal, pregnancy, postpartum

Introduction

Depression is a common problem among pregnant and postpartum women that presents women, their families, and care providers with unique assessment and treatment challenges. It is important to understand the epidemiology, etiology, risk factors, and consequences of depression during and after pregnancy in order to assess and intervene in a comprehensive and optimal manner. We emphasize strongly that we do not consider pregnancy or the postpartum period to be a pathological or medical condition, as are many of the other "comorbid" conditions discussed in this volume. However, pregnancy, labor and delivery, and postpartum transitions are biological and sociocultural events in a woman's life; they create a unique context that may complicate other medical or psychiatric problems, of which depression is one of the most common. In this chapter, we discuss current research on the epidemiology and psychopathology of perinatal depression and summarize clinical research on the assessment, intervention, and prevention of depression among pregnant and postpartum women. We highlight limitations to current research and outline recommendations for both future research and clinical practice.

Definitions and Epidemiology of Perinatal Depression

Pregnancy and parenting are normative events in a woman's life, as suggested by demographic data indicating that over 4 million women give birth each year in the United States, with a mean age for first birth of 25 years (Martin et al., 2011). Depression during pregnancy and postpartum is often stigmatized, given our cultural and historical emphasis on pregnancy and motherhood as the most fulfilling, joyful, and rewarding times in a woman's life. However, pregnancy, labor and delivery, and postpartum affect multiple psychological, social, and biological systems, such that the nature of the transition varies widely across time and from woman to woman.

Generally speaking, in the first trimester of pregnancy, a woman may expect to feel happy,

ambivalent, moody, or anxious, with normative physical symptoms including fatigue, nausea and vomiting, food cravings, discomfort, frequent urination, difficulty sleeping, and change in libido. Many women begin to experience an improvement in their physical symptoms during the second trimester, including decreased nausea and vomiting, and increased energy while also experiencing new symptoms associated with the rapid fetal growth that occurs during this trimester. Common emotional experiences include feelings of relief, impatience, and frustration. In late pregnancy women may expect to feel euphoric, forgetful, worried about weight gain and their baby's health, as well as more sensitive, while also experiencing physical symptoms of swelling, shortness of breath, increased fetal movement, and general aches and pains. The postpartum period is similarly a time of tremendous physical and psychological transition when a woman must recover from childbirth and adjust to motherhood. In addition to the significant physical and emotional changes accompanying pregnancy and the postpartum period, many women also experience changes and challenges in their social context, including social transitions in friendships and intimate partner relationships and role transitions at work and to becoming a parent.

In this chapter, we use the term *perinatal depression* to refer to an episode of major or minor depression that occurs during pregnancy or postpartum. Major and minor depression are defined as a two-week period during which one experiences depressed mood or anhedonia for most of the day nearly every day plus four additional symptoms for major depression or two additional symptoms for minor depression. This episode must be accompanied by clinically significant distress or impairment and is not better accounted for by use of drugs or medication, a general medical condition, or bereavement. Additionally, *perinatal depression* may be used to refer to elevated symptom severity. For example, much research on perinatal depression utilizes self-report measures of symptom severity with standardized cutoffs indicating likely depression. These measures differ from diagnostic measures in that they often assess a shorter period of time and do not require assessment of clinically significant distress or impairment. The phrase "the baby blues" is colloquially used to describe mild and transient sadness occurring after childbirth, in contrast to perinatal depression, which is more severe, distressing, and impairing. Although several terms and definitions for perinatal depression exist, we refer to the period of time prior to delivery as antenatal or pregnancy and the period of time after delivery as postpartum; both time periods are included in the period we refer to as perinatal.

According to the *Diagnostic and Statistical Manual of Mental Disorders IV Text Revision* (DSM-IV-TR), postpartum depression is defined as a major depressive episode occurring within four weeks after birth (American Psychiatric Association, 2000). The Mood Disorders Working Group for the DSM-5 is reconsidering the proximal bound time for the definition of postpartum onset (Wisner, Moses-Kolko, & Sit, 2010). Specifically, the Mood Disorders Working Group has recommended that the postpartum specifier be extended to six months. The duration of the antenatal and postpartum period studied by researchers varies widely, with much of their attention focused on the first year postpartum; where possible, we include information about the period of time assessed in presented research.

In a meta-analysis focusing on studies in developed nations that used a clinical assessment or structured clinical interview to confirm a diagnosis of major depression, Gavin and colleagues (2005) estimated point prevalence rates for major and minor depression to be 11% in the first trimester, and 9% in the second and third trimesters. In contrast, a separate meta-analysis of major and minor depression found a nonsignificant increase in prevalence rates over the course of pregnancy, beginning at 7% and increasing to 13% in the second trimester and then falling to 12% in the third trimester (Bennett, Einarson, Taddio, Koren, & Einarson, 2004). However, this meta-analysis differed from that of Gavin and colleagues by including studies that used self-report assessment of depression symptoms. Gavin and colleagues found that after delivery, point prevalence rates were the highest in the third month, at 13%, then dropping to 9.9% to 10.6% in the fourth through seventh months, and then to 7%. Period prevalence of major and minor depression was 19% in the first three months postpartum. Some research has found that depression may be more common during pregnancy than postpartum (Banti et al., 2011).

Prevalence estimates depend, to some degree, on the methods of assessment. Self-report severity measures often yield higher rates than diagnostic interview measures (Bennett et al., 2004; N. I. Gavin et al., 2005; O'Hara & Swain, 1996), with those having a greater focus on somatic symptoms yielding higher rates than those without a

focus on somatic symptoms (Bennett et al., 2004). Prevalence rates may also depend on the duration of the period assessed, with studies investigating a longer postpartum duration yielding higher prevalence rates (O'Hara & Swain, 1996). Race and ethnicity are also important considerations in understanding the prevalence of perinatal depression, as there are some indications of higher reported antenatal depression in black women and Latinas than in non-Hispanic white women (A. R. Gavin et al., 2011). However, other research has found both lower rates of elevated depressive symptom severity at delivery among African American, Hispanic, and other-race women compared with White women (Shen, Lin, & Jackson, 2010) and no differences in depressive symptom severity among African American and White women during pregnancy (Jesse, Walcott-McQuigg, Mariella, & Swanson, 2005). Further research is needed to understand the relationship of race and ethnicity to perinatal depression.

Few studies have compared rates of depression during the perinatal period with rates of depression in a comparison sample of women of childbearing age. Some research suggests that prevalence rates of diagnoses of major and minor depression do not differ between perinatal and nonchildbearing women but that depression symptom severity and impairment may be greater for perinatal women (O'Hara, Zekoski, Philipps, & Wright, 1990), while other research suggests that rates may be greater during the postpartum period. In a large, nationally representative study of individuals 18 to 50 years old containing a subsample of 14,549 women who reported a pregnancy during the previous year, postpartum women were at significantly higher risk for major depressive disorder compared with nonpregnant women (Vesga-Lopez et al., 2008). Although prevalence research focuses mainly on women meeting diagnostic criteria for major depression or exceeding a symptom severity cutoff, there is evidence that subclinical levels of depressive symptoms are associated with similar psychiatric comorbidity (e.g., anxiety), psychosocial stressors (e.g., stress, social support, maladaptive eating behaviors), and impairment (S. H. Goodman & Tully, 2009). In a sample of 79 pregnant women with a history of major depression, 30% met diagnostic criteria for a major depressive episode during pregnancy and 23% did not meet diagnostic criteria but had elevated depressive symptom severity on the Beck Depression Inventory-II (S. H. Goodman & Tully, 2009).

As is the case for depression in general, perinatal depression is highly comorbid with anxiety disorders (Andersson, Sundstrom-Poromaa, Wulff, Astrom, & Bixo, 2006; Le Strat, Dubertret, & Le Foll, 2011). In a population-based face-to-face survey, 1,524 women of 14,895 women of childbearing age reported being pregnant within the previous year (Le Strat et al., 2011). Participants completed a structured diagnostic interview for Axis I disorders. Approximately 43% of past-year depressed pregnant women had a comorbid anxiety disorder, compared with 11% of nondepressed past-year pregnant women. Depressed nonpregnant women had similar rates of anxiety disorder comorbidity, with about 45% having a concurrent anxiety disorder. A study of Swedish women who completed a diagnostic assessment during the second trimester and then at six months postpartum found that of those with a psychiatric diagnosis during pregnancy, about 20% met criteria for comorbid depression and anxiety during pregnancy and 23% during postpartum (Andersson et al., 2006). Andersson and colleagues found that depression and anxiety disorder diagnoses decreased significantly in the postpartum period as compared with the period of pregnancy. Le Strat et al. attribute the higher rates of comorbidity in their study compared with the Andersson et al. study to differences in measures and likelihood for higher false negatives in the Swedish sample.

In summary, evidence suggests that depression is at least as common if not more so during the perinatal period as it is among nonperinatal women of childbearing age. In addition, subthreshold depressive symptoms are even more common and are associated with significant adverse correlates.

Impact

The impact of depression during the perinatal period is substantial, with research suggesting important adverse correlates and consequences both for mother and offspring. Depression during pregnancy is associated with the development of preeclampsia, controlling for confounding factors (Kurki, Hiilesmaa, Raitasalo, Mattila, & Ylikorkala, 2000), which itself is associated with increased risk of maternal and fetal mortality. Depression during pregnancy also predicts miscarriage in women with a history of recurrent spontaneous abortions (Nakano et al., 2004). Compared with nondepressed women, women with untreated depression experience an increased risk of a variety of adverse obstetric outcomes, such as risk for epidural analgesia, operative deliveries (i.e., cesarean section and

instrumental vaginal delivery), and preterm birth (Grote et al., 2010); however, some research reveals no difference in rates of preterm births between untreated depressed and nondepressed women (Suri et al., 2007).

The majority of research on the impact of perinatal depression has focused on adverse effects on the development of the fetus, neonate, and infant (for a review see Field, 2011). Adverse effects for the fetus in women with symptoms of depression include excessive fetal activity (Dieter et al., 2001). Studies have reported increased risk for a range of adverse neonatal outcomes. A meta-analysis conducted by Grote and colleagues (2010) found that antenatal depression was significantly associated with low birth weight. In a study of 767 Chinese women, elevated self-reported depression symptom severity in the third trimester was significantly associated with admission to a neonatal care unit (Chung, Lau, Yip, Chiu, & Lee, 2001). A study of women in the third trimester of pregnancy living in rural Pakistan found poorer growth among infants of antenatally depressed versus nondepressed mothers (Rahman, Iqbal, Bunn, Lovel, & Harrington, 2004). Neonates of depressed mothers had significantly lower attention scores than neonates of depressed mothers taking a serotonin reuptake inhibitor and nondepressed mothers (Salisbury et al., 2011).

Infants of mothers depressed during pregnancy have demonstrated less responsiveness (e.g., to faces and sounds), habituation to mother's depressed affect, more crying, and disturbed sleep (Field, 2011). Infants of antenatally depressed mothers in a rural community in Pakistan demonstrated significantly more growth retardation at months 2, 6, and 12 and significantly more diarrheal episodes (Rahman et al., 2004) compared with infants of mothers who were not depressed during pregnancy. In a study of 247 women, antenatal self-reported depression as assessed by the Center for Epidemiological Studies Depression Inventory (CES-D) was significantly associated with mother-reported infant negative reactivity as measured by an eight-item version of the fear subscale of the Infant Behavior Questionnaire (IBQ) at two months postpartum (Davis et al., 2007).

A wide body of literature also suggests that children of depressed mothers experience a range of adverse behavioral and emotional outcomes. A recent review on the impact of maternal depression on children (though not specific to the perinatal depression) concluded that maternal depression significantly increases a child's risk of internalizing (e.g., depression, anxiety) and externalizing disorders (e.g., conduct disorder) and problems with the regulation of emotion more broadly (S. H. Goodman et al., 2011). The deleterious consequences of perinatal depression for both mother and offspring are significant and highlight the importance of understanding the nature of perinatal depression and employing efficacious treatment and prevention strategies.

Risk and Etiologic Factors

The etiology of perinatal depression is still uncertain and research continues to investigate psychological and physiological risk and resilience factors for women during this time. Research has identified multiple risk factors and potential causal pathways that increase women's chances of experiencing perinatal depression. Although no specific causal factors have been established (as is true of depression among general populations), a number of variables have been investigated, including psychopathology (e.g., depression and anxiety), interpersonal factors, and biology (e.g., hormonal sensitivity). There is great similarity between risk factors for perinatal depression and depression that occurs at other times in lives of women, including a history of depression and interpersonal stress (Kendler, Kessler, Neale, Heath, & Eaves, 1993).

Numerous studies have revealed history of depression as a robust predictor of risk for postpartum depression (Beck, 2001; Bloch, Rotenberg, Koren, & Klein, 2006), as is true for depression in women generally (Kendler et al., 1993). In a study of 3,472 women waiting for antenatal care visits in obstetrics waiting rooms, 20% scored above the cutoff for depression on the Center for Epidemiological Studies-Depression scale (CES-D). Women who reported a history of depression were 4.9 times more likely to have an elevated CES-D score (Marcus, Flynn, Blow, & Barry, 2003). History of depression may also predict subclinical levels of perinatal depression. In a study of 1,300 women assessed in the first three days after delivery, those with a history of depression were significantly more likely to have elevated scores on the Edinburgh Postnatal Depression Scale (EPDS) (Bloch et al., 2006). In a study of primiparous women with a history of at least one major depressive episode, 30% met DSM-IV criteria for a major depressive episode during pregnancy and 23% exceeded the BDI-II cutoff for a major depressive episode but did not meet diagnostic criteria (S. H. Goodman & Tully, 2009); these figures represent stark elevations in

risk compared with the rates of depression observed among unselected samples of perinatal women reviewed earlier. Finally, depression during pregnancy also increases women's risk of depression during the postpartum period (Beck, 2001).

Research on other psychopathology risk factors for perinatal depression has emphasized the role of anxiety, mainly focusing on the relationship between antenatal anxiety and postpartum depression. A study of 748 women in the final trimester of pregnancy found that women with high self-reported worry were almost three times more likely to have elevated depressive symptoms on the EPDS at eight weeks postpartum (Austin, Tully, & Parker, 2007). Antenatal anxiety appears to be a risk factor for depressive symptoms past the early postpartum period. Self-reported anxiety at both 18 and 32 weeks of gestation predicted elevated scores on the EPDS at 8 weeks and 8 months even when controlling for antenatal depression (Heron et al., 2004).

A study of 497 French pregnant women found that nearly a quarter met DSM-IV criteria for an anxiety disorder, and women with an anxiety disorder diagnosis were approximately three times more likely to score above a 12 on the EPDS at postpartum, even controlling for a diagnosis of major depression (Sutter-Dallay, Giaconne-Marcesche, Glatigny-Dallay, & Verdoux, 2004). Research examining the time course of the relationship between anxiety and depression has found a bidirectional effect, with depressive symptoms in early pregnancy predicting increases in anxiety symptoms in late pregnancy, and late pregnancy anxiety symptoms predicting depressive symptoms in the early postpartum period (Skouteris et al., 2009). Thus research has clearly implicated self-reported and diagnostic anxiety as a risk factor for perinatal depression. The overall pattern of anxiety conferring risk for perinatal depression is evident in examining specific anxiety disorders. For example, a study of 600 Italian women who were followed from their first trimester of pregnancy through six months postpartum found that a history of panic disorder and family history of panic disorder were significant risk factors for developing postpartum major or minor depression, controlling for previous and current depression (Rambelli et al., 2010).

The interpersonal domain is important to consider as a potential contributing factor to depression throughout the life span, and specifically during the perinatal period. Research suggests that stress during pregnancy increases the risk of postpartum depression (Beck, 2001; Robertson, Grace, Wallington, & Stewart, 2004). Interpersonal stress—including low social support, lack of marital support, and less satisfying relationship with a husband or partner—is associated with increased risk of perinatal depression (S. H. Goodman & Tully, 2009; Rich-Edwards et al., 2006).

In addition to psychopathology and interpersonal risk factors, a meta-analysis of 84 studies yielded seven additional significant risk factors for postpartum depression (Beck, 2001). Self-esteem, child-care stress, infant temperament, and maternity blues had medium effect sizes. Marital status, socioeconomic status, and unplanned/unwanted pregnancy had small effect sizes.

Many theories of perinatal depression emphasize the role of biological factors. In particular, biological theories emphasize differential sensitivity to hormonal fluctuations (Soares & Zitek, 2008). Based on the observation that development of depression in the postpartum period predicts depression in subsequent pregnancies, Bloch and colleagues hypothesized that hormonal events specific to the perinatal period may be responsible for development of perinatal depression in a subgroup of women (Bloch et al., 2000). Specifically, estradiol and progesterone levels increase during pregnancy and drop rapidly during the postpartum period (Bloch, Daly, & Rubinow, 2003). However, there are no consistent differences in baseline hormonal levels between women with and without postpartum depression (Bloch et al., 2003). Bloch and colleagues (2000) simulated hormonal conditions in pregnancy and delivery by administering estradiol and progesterone for eight weeks and then rapidly withdrawing them. When the hormones were withdrawn, women with a history of postpartum depression (but no history of nonperinatal depression) experienced a significant increase in depressive symptoms compared with women without a history of psychiatric illness, suggesting an increased sensitivity to abrupt changes in gonadal steroid levels. A randomized controlled trial of 61 women with major depression that developed within three months of delivery and persisted for as long as 18 months found that women randomized to receive transdermal estradiol experienced significant and rapid improvement in depression symptoms compared with women randomized to placebo (Gregoire, Kumar, Everitt, Henderson, & Studd, 1996), providing further evidence of the role of hormones in the development and maintenance of depression in the perinatal period.

Corticotropin-releasing hormone (CRH) has also been hypothesized to be implicated in the development of perinatal depression owing to its possible role in the development of depression across the life span and its rapid withdrawal after delivery of the placenta (Yim et al., 2009); however, results are inconsistent. Elevated placental CRH at 25 weeks gestational age was a strong predictor of elevated depressive symptoms at postpartum, controlling for concurrent depressive symptoms (Yim et al., 2009). Other research has found that midpregnancy CRH was not associated with postpartum depression (Meltzer-Brody et al., 2011; Rich-Edwards et al., 2008). Elevated CRH at midpregnancy was associated with antenatal depression in one study (Rich-Edwards et al., 2008) but not in another (Meltzer-Brody et al., 2011).

Recent research has also pointed to the potential role of inflammatory processes. For example, after childbirth, physiological conditions that are autoimmune in nature can flare up, leading researchers to hypothesize that some cases of perinatal depression could be caused by autoimmune response (Gleicher, 2007). In addition, recent studies have examined the role of iron deficiency in postpartum depression. Specifically, low ferritin concentration during the immediate postpartum period is associated with postpartum depression (Albacar et al., 2011). The depletion of iron during pregnancy and the postpartum period could impact neurotransmitter and myelin metabolic pathways, increasing the risk of perinatal depression. Recent research also suggests that the hypothalamic-pituitary-adrenal(HPA) axis, the common stress pathway, may play a role in the etiology of postpartum depression (Labad et al., 2011; O'Keane et al., 2011).

In all likelihood, an integrated model of perinatal depression is necessary to understand the complex interplay of psychological, social, and biological processes. To date the field has identified a number of important correlates and risk factors for perinatal depression, although no specific causal factors have been established. Understanding depression during pregnancy requires consideration of the multiple and changing biopsychosocial contexts in which depression occurs. More research is needed to identify etiological factors and to use such knowledge to inform the development of more powerful prevention and intervention programs.

Assessment

Assessment of perinatal depression has utilized both self-report and interview measures. Standard self-report measures of depression symptom severity (e.g., BDI, CES-D) are frequently used to screen for depression during the perinatal period. The Edinburgh Postnatal Depression Scale (EPDS) (Cox, Holden, & Sagovsky, 1987) is a self-report measure designed to measure depression specifically in the postnatal period and frequently used to assess depression during pregnancy. The EPDS was developed upon observation that self-report measures frequently yielded false positives of depression when compared with diagnostic assessments, perhaps because of their emphasis on somatic symptoms. The EPDS comprises 10 items, with possible scores ranging from 0 to 30. Sensitivity, specificity, and positive predictive values were adequate in two postpartum samples (Cox et al., 1987; Murray & Carothers, 1990) and the EPDS was sensitive to change, as confirmed by a comparison with diagnostic criteria (Cox et al., 1987). Validation studies in English-speaking women cite 13 as the optimum cutoff score for screening major depression in postpartum women and 15 for antenatal women (Matthey, Henshaw, Elliott, & Barnett, 2006).

Antenatal and postpartum women frequently visit health-care settings for routine antenatal care and infant checkups. Thus these visits are an optimal time to use brief screening assessments for perinatal depression. Screening assessments such as the EPDS are brief and can easily be completed in the waiting room. Women who score above a cutoff can be flagged for follow-up during their visits. It is likely important to follow up an elevated score with a more detailed interview to confirm a diagnosis and evaluate possible comorbidities, such as anxiety, and to assess for bipolar disorder. Health-care providers may be limited in the time or training they have to conduct a more detailed assessment and thus should be able to refer the patient to a clinic where she can receive adequate assessment and intervention.

Although screening for depression and further follow-up seem obvious initial steps to providing intervention for depression or prevention of symptom worsening, research has shown that many antenatal women may not find this to be an acceptable approach. In one study, 93% of 400 women agreed to complete a self-report depression screening using the EPDS, which included an additional question asking whether they agreed to be contacted by a research coordinator if their scores indicated probable depression (Carter et al., 2005). Of the women who completed the report, 13% scored above 12, suggesting probable depression. However, only 31% of those women agreed to contact from the

study coordinator. Seven attended an interview to confirm the diagnosis of depression, and six were eligible to participate in a study comparing CBT to routine clinical care (RCC). Of the three randomized to CBT, only one began therapy. One question is whether the low rates of treatment initiation may be due to the randomized controlled design of the study. However, other research has found similar effects in nonrandomized controlled designs (Robinson & Young, 1982; Tam, Newton, Dern, & Parry, 2002). This body of research suggests that future research is needed to optimize widespread screening and increase likelihood that screening will lead to access to treatment for perinatal women who may be depressed.

One potential limitation of standard self-report and interview measures of depression is that they often include items assessing somatic symptoms that are also common during the perinatal period (e.g., appetite disturbance, sleep disturbance, fatigue, weight change, focus on physical health) (Kamysheva, Wertheim, Skouteris, Paxton, & Milgrom, 2009; Zib, Lim, & Walters, 1999). A version of the Structured Clinical Interview for DSM Disorders (SCID) (i.e., SCID-PND) has been adapted (e.g., removal of modules not relevant to study aims) and validated in a sample of perinatal women in eight countries (Gorman et al., 2004). However, to our knowledge, there is not currently a gold-standard interview measure for the perinatal period that accounts specifically for the risk of conflation. Using depression interview measures not validated for use during the perinatal period may be problematic if use results in underdiagnosis when symptoms of depression may be incorrectly attributed to normative somatic changes of the perinatal period or overdiagnosis when normative somatic changes of the perinatal period are incorrectly attributed to symptoms of depression.

There are several possible approaches to using interview measures to assess perinatal depression. One approach is to rate symptoms "as you see them," minimizing the need to rely on clinical judgment to discern whether a somatic symptom is due to pregnancy or depression. A limitation of this approach is illustrated by a clinical example. Consider a nondepressed woman in her eighth month of pregnancy assessed using the Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960). By endorsing waking frequently in the night to use the bathroom, frequent and bothersome need to urinate, appetite increase and specific cravings, feeling fatigued and heaviness in certain parts of her body, a focus on her physical health, and weight gain, she would receive a minimum score of six on the HAM-D in the complete absence of mood symptoms. Hamilton (1960) encouraged interviewers to "use all information available to help him with his interview and in making the final assessment" (p. 56), and thus the "rate it as you see it" approach may not be fitting with the original goals of this and other interview measures.

Research on the use of the HAM-D in pregnancy has demonstrated that somatic items do not appear to be strongly associated with a major depressive episode (Altshuler et al., 2008). Though research with nondepressed and depressed perinatal women has demonstrated high correlation between HAM-D total scores and measures that omit somatic items, evidence suggests that somatic items do not correlate with total score during pregnancy (Ross, Gilbert Evans, Sellers, & Romach, 2003). Kammerer and colleagues investigated the hypothesis that certain DSM-IV depression symptoms would not be associated with major or minor depression diagnosis in pregnant and postpartum (through six weeks) women (Kammerer et al., 2009). Interviewers administered a SCID, modified so that participants responded to all items, regardless of whether they met the gateway criteria of depressed mood and anhedonia. Interestingly, depressed and nondepressed women did not differ in their endorsement of the appetite item, suggesting that appetite may not be a valid symptom of depression during the perinatal period.

Another approach may be to modify existing interview measures to account for pregnancy and postpartum-related somatic symptoms. One might decide not to score symptoms that are unequivocally caused by or related to pregnancy and postpartum, like expected weight gain (during pregnancy) or loss (during postpartum). However, it is often difficult to assess whether a symptom is exclusively related to pregnancy or postpartum factors. Affonso, Lovett, Paul, and Sheptak (1990) modified the Schedule for Affective Disorders and Schizophrenia (SADS) to differentiate pregnancy and postpartum symptoms from perinatal clinical depression. The SADS-Pregnancy and Postpartum Guidelines (SADS-PPG) included questions to clarify the nature and course of depression symptoms in perinatal women. Interviewers recorded participants' SADS score (i.e., without consideration of perinatal status) and SADS-PPG score. Over half of the items had significantly higher scores on the SADS than the SADS-PPG. The SADS-PPG identified

women who met diagnostic criteria for depression. However, to our knowledge, no other studies have reported use of this measure in a perinatal sample.

A third approach might be to create a new interview measure tailored for the perinatal period. There is a precedent for creating new depression measures for important developmental phases. For example, the Childhood Depression Rating Scale was based on the HAM-D but tailored for the developmental level of children (Poznanski, Cook, & Carroll, 1979). The Geriatric Depression Scale was created because existing measures of depression often failed to differentiate between dementia and depression and overemphasized somatic symptoms common in older adulthood (Yesavage et al., 1983). A perinatal measure that assists in differentiation between somatic symptoms of pregnancy versus depression may improve assessment. However, this approach might be less appropriate for longitudinal studies that follow perinatal women beyond the point at which it would make sense to use a measure specific to the perinatal period.

Intervention and Prevention

Depression during pregnancy and the postpartum period presents women, their families, and their care providers with complex clinical decisions. Although pregnant women in particular have been excluded from much of the clinical research on interventions for depression, there is an emerging literature that informs clinical practice with pregnant and postpartum depressed women. Here, we review current research on intervention and prevention strategies.

Antidepressant Medication Treatment for Perinatal Depression

Multisite research conducted in the United States reveals that 7% of women received a prescription of antidepressant medicine (ADM) during pregnancy, with SSRIs being the most common type of ADM prescribed (Andrade et al., 2008). Despite the prevalence of use, not a single randomized controlled trial has been conducted to investigate the efficacy and safety of ADM during pregnancy, and only one trial currently in progress focuses on postpartum women (Pearlstein et al., 2006).

Decisions about the use of ADM during pregnancy and postpartum are complicated primarily by concerns about potential adverse impacts on the fetus or nursing infant. However, research in this area has been conflicting and difficult to interpret given that most studies do not control for the impact of depression itself. Thus it has been difficult to ascertain whether adverse effects on offspring are due to exposure to pharmacological agents, to depression, or to a combination of these. Possible adverse effects include miscarriage (Yonkers, et al., 2009), increased risk of prematurity and reduced head circumference (El Marroun et al., 2012), lower quality of movement scores and more sympathetic nervous system stress signs as neonates (Salisbury et al., 2011), higher serotonergic adverse behavioral effects (e.g., tremor, restlessness, rigidity) in the first four days of life, and significantly lower 15-minute APGAR scores compared with neonates not exposed to an SSRI (Laine, Heikkinen, Ekblad, & Kero, 2003). Some research suggests that the risk for adverse behavioral symptoms may be greater for neonates exposed to an SSRI later in pregnancy but also suggests that such symptoms can be managed well with supportive care for the neonate after delivery (Moses-Kolko et al., 2005). In a recent controversial study, women who were prescribed an SSRI early in pregnancy were significantly more likely to have a child diagnosed with an autism spectrum disorder (ASD) compared with those not prescribed an SSRI even when controlling for history of psychiatric diagnosis. Nevertheless, rates of an ASD diagnosis were low (< 3%) (Croen, Grether, Yoshida, Odouli, & Hendrick, 2011). Other studies have linked ADM use to adverse effects among breastfeeding infants, including reduced alertness, constipation, sleepiness, and irritability (Costei, Kozer, Ho, Ito, & Koren, 2002).

Women report concerns about antidepressant medication treatment during pregnancy and while breastfeeding (Dennis & Chung-Lee, 2006; J. H. Goodman, 2009), most likely owing to fear about possible side effects to the fetus or breastfeeding infant, and many choose to discontinue use of an ADM upon a pregnancy diagnosis (Ramos, Oraichi, Rey, Blais, & Berard, 2007). Continuing or initiating ADM use during pregnancy or while breastfeeding may confer some risk, but cessation of antidepressant medication use during pregnancy is also risky, with research showing that 68% of those who discontinued ADM relapsed during pregnancy, compared with 26% who relapsed while on antidepressant medication (Cohen et al., 2006).

Psychotherapy for Perinatal Depression

Psychotherapy is a promising treatment strategy for women with perinatal depression because of its low side-effect profile, efficacy in the general

population, and women's self-reported concerns about use of ADM during pregnancy or breastfeeding. Qualitative reviews and survey research reveal that talk therapy is the preferred treatment option among pregnant women (Dennis & Chung-Lee, 2006; J. H. Goodman, 2009).

Research on psychotherapy for perinatal depression has focused mainly on cognitive behavioral therapy (CBT) and interpersonal psychotherapy (IPT). Research demonstrates that CBT, when adapted for rural communities in Pakistan and administered by primary health providers, was associated with higher rates of recovery from postpartum depression at 6 and 12 months compared with enhanced routine care (Rahman, Malik, Sikander, Roberts, & Creed, 2008).

Preliminary studies investigating interventions incorporating CBT elements and tailored for the postpartum period demonstrate efficacy compared with routine clinical care (Honey, Bennett, & Morgan, 2002). Postpartum women with elevated EPDS scores who were randomly assigned to psychoeducation with a CBT group demonstrated significant reduction in symptom severity after the eight-week intervention through six weeks postintervention compared with women randomized to routine clinical care (Honey et al., 2002). Similarly, women with postpartum depression who were randomized to a 10-week group treatment incorporating CBT elements showed significant improvement in depression scores over time and compared with a waitlist control group (Meager & Milgrom, 1996). However, participants in both studies did not experience improvements in other areas of psychological functioning and well-being, including coping, social support, marital relationships, parenting stress, or self-esteem (Honey et al., 2002; Meager & Milgrom, 1996).

Although CBT may outperform routine care or a waitlist control, it may not outperform other psychological interventions. In an Australian study, 192 antenatal women meeting DSM-IV criteria for depression were randomized to receive routine clinical care, group-based CBT, group-based counseling, or individual counseling (Milgrom, Negri, Gemmill, McNeil, & Martin, 2005). Women in the three psychological interventions experienced significantly greater decreases in symptom severity than women receiving routine care, although those in the CBT and counseling groups did not differ.

Recent work has adapted CBT to community-based settings. CBT has been integrated into home visitation programs with great benefit. Twenty-six first-time mothers who were generally young, unmarried, and low-income received up to 17 weekly hour-long sessions (Ammerman et al., 2005). Participants experienced significant reductions in symptom severity and functional impairment, significant improvement in positive attitudes toward motherhood, and 85% fully or partially remitted from major depression.

Meta-analysis indicates that studies including an IPT intervention had significantly larger effect sizes than including a CBT intervention (Sockol, Epperson, & Barber, 2011). A pilot study of 13 antenatal women meeting DSM-III criteria for major depression demonstrated significant reductions in depression symptoms over the course of 16 weeks of IPT (Spinelli, 1997). In a sample of mostly White and well-educated women, those randomly assigned to IPT had a greater decrease in symptom severity and were more likely to respond to treatment, to recover, and to no longer meet criteria for major depression compared with women randomized to a waitlist control group (O'Hara, Stuart, Gorman, & Wenzel, 2000). Additionally, women in the IPT group experienced significantly greater improvements in psychosocial functioning.

IPT appears to also be effective for women with little social support and low socioeconomic status (Spinelli & Endicott, 2003). Antenatal women of low socioeconomic status with elevated depressive symptom severity who were randomized to an IPT group evidenced significantly greater reductions in depressive symptoms and improvements in social functioning prior to delivery and at six months postpartum compared with women randomized to enhanced clinical care (Grote et al., 2009). Women receiving IPT also appear to achieve greater clinical benefit compared with a matched intervention. In a randomized controlled trial comparing IPT and a matched parenting education program, depressed perinatal women receiving IPT demonstrated significantly greater symptom improvement and higher rates of recovery (Spinelli & Endicott, 2003). Because of its focus on role transitions and interpersonal relationships, IPT may be particularly well suited for depressed perinatal women.

Prevention of Perinatal Depression

Prevention of perinatal depression may avert the obstetric, neonatal, and developmental risks associated with untreated and ADM treated depression. Despite the potential short and long-term benefits for women and their offspring, research into relapse

prevention strategies for perinatal women is only in its nascent stages.

A number of studies have focused on prevention interventions for high-risk, low-income women. Women receiving public assistance who were at risk for developing postpartum depression were randomly assigned to treatment as usual or a four-session group intervention based on IPT. Women in the IPT group evidenced significantly greater changes in depression symptom severity over the course of the intervention and were significantly less likely to develop depression through three months postpartum (Zlotnick, Johnson, Miller, Pearlstein, & Howard, 2001).

CBT has been adapted for administration in group format for low-income women at high risk for depression. Antenatal Central American immigrants randomized to an eight-week CBT group demonstrated significantly lower depressive symptoms compared with women randomized to usual care immediately after the intervention but not during the postpartum period (Le, Perry, & Stuart, 2011). Relapse rates did not differ between the groups, which may be due to the generally low rates of clinical depression over the course of the study and other methodological factors. A separate study adapting CBT for women enrolled in home visitation programs found that those randomized to the preventive intervention demonstrated significantly lower symptom severity and rates of major depressive episode (as measured by the Maternal Mood Screener) compared to women randomized to control at three months postintervention (Tandon, Perry, Mendelson, Kemp, & Leis, 2011).

A pilot study of antenatal Korean women with elevated depression symptom severity found that women randomized to individual CBT tailored for the antenatal period had significantly lower depression scores and marital dissatisfaction at one month postpartum compared with a control group (Cho, Kwon, & Lee, 2008). However, a study in which women with elevated symptom severity or a history of depression were assigned to receive group CBT or a psychoeducational booklet found significant improvement in depression symptom severity over time but no differences between groups (Austin et al., 2008).

Other research provides support that psychoeducation may be useful in preventing depression. In a study of low-income, Mexican pregnant women at high risk for depression due to a history of depression or elevated symptom severity, 127 were randomized to treatment as usual and 250 were randomized to a group intervention (Lara, Navarro, & Navarrete, 2010). The group intervention consisted of an educational component about the perinatal period and risk factors for depression and a psychological component that increased positive thinking, self-esteem, self-care, and participation in pleasurable activities. Women in the intervention group had significantly lower rates of a depression diagnosis and no difference in symptom severity at postpartum (six weeks and four to six months) compared with women in the treatment as usual group.

Antidepressant medication may also be an effective prevention strategy. Formerly depressed women were randomly assigned to receive sertraline or placebo soon after delivery and followed for 17 weeks (Wisner et al., 2004). Women assigned to sertraline were less likely to experience a recurrence of depression, and time to recurrence was significantly longer compared with the placebo group. However, owing to potential adverse effects of ADM and women's reluctance to use ADM while pregnant or breastfeeding, ADM may be a less acceptable prevention strategy.

To date, very little perinatal depression research has focused on interventions created for the primary purpose of preventing relapse. Mindfulness-based cognitive therapy (MBCT) (Segal, Williams, & Teasdale, 2002) is a relapse-prevention approach that incorporates mindfulness meditation with cognitive therapy to specifically target vulnerability among formerly depressed individuals. Five large randomized clinical trials support the efficacy of MBCT among individuals with highly recurrent depression (Godfrin & van Heeringen, 2010; Kuyken et al., 2008; Ma & Teasdale, 2004; Segal et al., 2010; Teasdale et al., 2000). Preliminary results from an ongoing study suggest that MBCT is associated with high satisfaction and positive changes in depressive severity among pregnant women with histories of depression (Dimidjian & Goodman, 2010). Another pilot study incorporating elements of MBCT for women in their second or third trimester previously treated for mood concerns also suggests that pregnant women find this intervention to be associated with high acceptability and clinical benefit (Vieten & Astin, 2008).

Barriers to Treatment

Despite the fact that assessment strategies as well as pharmacological and nonpharmacological interventions exist, few depressed perinatal women receive treatment. For example, although 20% of women in an obstetrics clinic scored above the CES-D cutoff for depression, only 14% of those

women reported receiving any formal treatment for depression (Marcus et al., 2003). Research reveals several barriers to treatment, including lack of knowledge about postpartum depression, not knowing where to obtain services, fear of stigma, perceived lack of time, and normalization or minimization of symptoms by health-care professionals (Dennis & Chung-Lee, 2006; J. H. Goodman, 2009).

Research on barriers to care suggests that psychoeducation about perinatal depression may be an important first step for women to initiate treatment. Specifically, information about the signs, symptoms, prevalence, and risks for perinatal depression may improve the ability of women, friends, family, and practitioners to notice perinatal depression and reduce stigma. Referral information that includes options for care and information about the typical time commitment and cost of each may increase knowledge about where to obtain services and realistic expectations about obtaining care. Indeed, research suggests that women with elevated EPDS scores were significantly more likely to seek treatment when their physician discussed depression with them (Flynn, O'Mahen, Massey, & Marcus, 2006).

To summarize, research shows that most pregnant and postpartum women prefer psychotherapy to ADM, most likely for fear of adverse effects of antidepressant medication on a fetus or breastfeeding infant. Generally speaking, ADM may be associated with obstetric, neonatal, and developmental adverse effects, many of which may be temporary and easily managed. Untreated depression and discontinuing ADM is also risky. Psychotherapy demonstrates efficacy during the perinatal period, with IPT appearing to be particularly suited for women, perhaps because of its emphasis on role transition and interpersonal factors. However, more rigorous randomized controlled trials are needed to assess the efficacy of CBT as well as a greater range of therapies, like behavioral therapy, mindfulness interventions, and complementary and alternative medicine (CAM). Research into prevention strategies is even sparser, despite the identification of several robust risk factors, such as a history of depression. Conceptualizing depression during the perinatal period as unique from depression during the life span in general may be useful in the development of more targeted, parsimonious, and acceptable intervention and prevention strategies.

Future Research Directions

While prevalence research has made great strides in demonstrating the common occurrence of perinatal depression, particularly in women with a history of depression, research is needed to incorporate more diverse samples. Additionally, it is a popular belief that depression is more common among pregnant and postpartum women than among women of childbearing age who are not postpartum. Although research on this topic is mixed, it is clear that the impact of depression during this sensitive life-cycle stage may be more extensive and enduring. At least one study also shows that women with subclinical depression suffer from a level of impairment that is similar to that of women who meet the full diagnostic criteria for depression during pregnancy or postpartum (S. H. Goodman & Tully, 2009). Future research should also elucidate the prevalence rates of subclinical depression.

Continued investigation of the impact, risk factors, and theories of etiology of perinatal depression will help to develop a more thorough understanding of this disorder. Future research should examine how specific combinations of risk factors work together to increase women's likelihood of developing depression. Excessive anxiety is a significant risk factor for perinatal depression, although future research should investigate whether some particular anxiety disorders confer greater risk than others. Further investigation of the theories of development or causal pathways involved in perinatal depression would highlight opportunities for targeted prevention and intervention strategies.

Improving the means by which we detect perinatal depression should lead to more accurate prevalence estimates. Future research may investigate whether women's participation in screening and intervention efforts depends on the location or context of screening, the burden of the intervention, or whether they have established a relationship with the health-care provider in completing screening, confirming diagnosis, or providing mental health care. More research is needed on interview measures for perinatal depression. Important questions include whether the current gold standards are appropriate for use during the perinatal period or possibly lead to overdiagnosis or underdiagnosis. Would follow-up questions specific for pregnant or postpartum women improve the accuracy of diagnosis or do we need a new interview measure specifically for the perinatal period?

Dimidjian and Goodman (2009) outline several possible future research directions for intervention research. There is a dearth of research on nonpharmacological interventions for perinatal women, despite the fact that psychotherapy being perinatal

women's top treatment preference. Several interventions—including cognitive behavior therapy, behavioral activation, and interpersonal psychotherapy—have been proven effective for the treatment of acute depression in a general sample, and a growing body of research is investigating their efficacy in pregnant and postpartum samples. This area of study would benefit from more rigorous randomized trials utilizing adequate controls. In addition, the field would greatly benefit from comparative efficacy trials testing ADM and psychotherapy. Rigorous comparisons of ADM and psychotherapy may help to clarify and inform the complex decision-making process for perinatal women and their health-care providers. Finally, a wider variety of interventions deserve empirical scrutiny with this population, including CAM interventions. Several CAM treatments have been investigated both as monotherapies and adjunctive treatment for the perinatal period, including omega-3 fatty acids, exercise, folate, bright light therapy, St. John's wort, and *S*-adenosyl-methionine (SAM-e) (for a review see Freeman, 2009). Some research suggests the efficacy of these treatments, but more rigorous study is needed to ascertain both the safety profile and efficacy of these treatments for perinatal depression. Finally, given the adverse effects of perinatal depression, research establishing effective psychosocial prevention approaches will continue to be important for the field as well.

Clinical Guidelines for Practitioners

Assessment

Practitioners working with antenatal and postpartum women should consider the unique psychiatric and psychosocial features of the period, including, for example, increased somatic symptoms, impairment, and stigma. Practitioners, including obstetrician gynecologists and pediatricians, should also take advantage of women's routine antenatal and infant checkups and make screening for elevated depressive symptom severity a standard practice. In a presentation on responsible postpartum depression screening (Wisner, 2007), expert Katherine Wisner recommended that practitioners screen for postpartum depression at the first postnatal appointment and confirm a diagnosis with a standard diagnostic instrument. Similarly, practitioners may screen for postpartum depression at the first antenatal visit and throughout pregnancy. Additionally, Wisner recommends that practitioners refer depressed patients to a mental health professional quickly and then follow up.

Practitioners should carefully monitor patients known to have risk factors for developing perinatal depression, including a history of past depression, anxiety, interpersonal stress, and low socioeconomic status. In addition, although concerns about pregnancy, delivery, and parenting are typical and adaptive during pregnancy, research suggests that excessive and uncontrollable anxiety may be common and confer risk for developing perinatal depression. Thus clinicians should simultaneously assess for both history of and current anxiety and depression.

The EPDS is an obvious choice as a screening strategy because it is brief and was developed with an eye to the unique consideration of depression during the perinatal period. Practitioners using the EPDS as a screening or assessment tool should be aware of the recommended cutoffs. It has been recommended that a score of 13 or more should be used to report probable major depression in postpartum women, and 15 or more for antenatal women (Matthey et al., 2006). Other options for screening instruments include the BDI, Postpartum Depression Screening Scale (PDSS), and CES-D (Gaynes et al., 2005). The Patient Health Questionnaire (PHQ-9: Kroenke, Spitzer, & Williams, 2001), which is based on the duration and symptom criteria of the DSM-IV-TR (American Psychiatric Association, 2000), is also a brief self-report measure that may be useful in perinatal depression screening. Research comparing the psychometric properties and ability to detect clinician-diagnosed major depressive disorder in a psychiatry outpatient sample of perinatal women found few differences between the PHQ-9 and EPDS (Flynn, Sexton, Ratliff, Porter, & Zivin, 2011).

As outlined above in the discussion of assessment, practitioners are advised to consider how somatic symptoms in a pregnant or postpartum patient (e.g., appetite disturbance, sleep disturbance) may be easily confounded with the somatic symptoms of depression. Practitioners are warned against assuming that somatic symptoms are due primarily to the antenatal or postpartum status of the patient, which may lead to underdetection of depression. On the other hand, practitioners are also warned against assuming that somatic symptoms are due primarily to a mood episode, which may lead to false positives. Questions probing whether somatic symptoms ebb and flow with mood or remain stable despite remittance or worsening of depression symptoms may help to elucidate their likely origin.

Treatment

In 2010, the American Psychiatric Association (APA) and American College of Obstetricians and Gynecologists (ACOG) published a report with guidelines for managing depression for women who are preconception, pregnant and not receiving pharmacotherapy, or pregnant and receiving pharmacotherapy (Yonkers et al., 2009). The APA and ACOG recommend that preconception women with moderate to severe symptoms be treated aggressively by a psychiatrist and wait several months to achieve stability on an ADM before attempting to conceive. In fact, the APA (2010) also recommends that because many pregnancies are unplanned, psychiatrists should discuss the risks and benefits of ADM-treated versus untreated depression in all women with childbearing potential regardless of intention to become pregnant. Patients who have achieved a several-month period of euthymia on ADM may be recommended for ADM taper and discontinuation before conception. The APA and ACOG recommend that psychiatrists avoid using newer-generation ADMs, for which there is less information about reproductive safety. The APA and ACOG emphasize the necessity of assessing a currently untreated pregnant woman's preferences for intervention. A woman preferring to avoid pharmacotherapy may benefit from psychotherapy. For women open to using ADM, a psychiatrist should consider gestational age and ADM safety profiles. For a woman who is currently taking ADM during pregnancy, the APA and ACOG again recommend aggressive treatment for those patients with severe symptoms and a discussion of risks and benefits of medication continuation versus discontinuation for women with more mild symptoms. The APA and ACOG suggest that psychiatrists may recommend psychotherapy for symptomatic women to replace or augment pharmacotherapy. Although not reviewed as an intervention strategy in the current chapter, both the APA (2010) and APA/ACOG (2010) practice guidelines suggest electroconvulsive therapy as a treatment option for women who are unresponsive to ADM or psychotherapy and suffer from severe, suicidal, or psychotic depression.

An American Psychological Association (2010) practice guideline for the treatment of patients with major depressive disorder recommends that psychotherapy be considered as a treatment option for the perinatal period whenever possible. Indeed, research shows that most women prefer psychotherapy alone (Dennis & Chung-Lee, 2006; J. H. Goodman, 2009) or in combination with ADM (Patel & Wisner, 2011).

Although a combined medication and psychotherapy approach may be recommended in the general population for milder presentations, a surveyed group of experts recommended the use of ADM with psychotherapy only for severe cases while trying to conceive or during pregnancy (Altshuler et al., 2001). A meta-analysis researching ADM effects in a general population supports its use primarily for very severe cases: participants receiving ADM or pill placebo did not differ in symptom improvement except for patients with very severe depression (Fournier et al., 2010).

In conclusion, research shows that women value taking an active and collaborative role in treatment decisions during pregnancy and postpartum (Patel & Wisner, 2011). Thus practitioners should engage patients in a risk-benefit discussion considering (but not limited to) a woman's treatment preferences, severity of symptoms and psychiatric history, stage of pregnancy, whether she is breastfeeding or plans to do so, risks of untreated depression versus treated depression, current research on different intervention strategies, and current (though limited) research on the acute and long-term effects of untreated and treated depression.

Summary

Pregnancy, labor, delivery, and postpartum transitions are biological and sociocultural events in a woman's life; they create a unique context that may complicate the experience, detection, and treatment of depression. During assessment, clinicians are faced with the challenge of considering how the perinatal period affects the manifestation of symptoms. In considering treatment options, a clinician must engage in a collaborative decision-making process with each patient to consider her history, symptom severity, and preferences while also keeping in mind the growing body of research on risks, benefits, and efficacy of various treatment options for both mother and child. Research into the epidemiology, etiology, and evidence-based assessment and treatment of perinatal depression can have a significant impact on the lives of women, their children, and their families.

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CHAPTER

31 Multidisciplinary Treatments and Medications for Depressive Disorders and Comorbidity

Robert H. Howland

Abstract

Compared with episodic depression, chronic depression and treatment resistant depression (TRD) have higher rates of comorbidity, more persistent social and vocational disability, an increased risk of suicide, greater medical morbidity and mortality, and greater health-care utilization and costs. A large number of antidepressant medications and other psychotropic drugs, depression-focused psychotherapies, and neuromodulation therapies are available for the treatment of depression. Many drugs or psychotherapies are used for the treatment of other psychiatric disorders or medical conditions, and they should be considered relevant when these comorbidities exist with depression. Selecting treatments for depression must take into account the clinical implications of the presence of any comorbidities. Because comorbidity is associated with depressive chronicity and treatment resistance, various approaches to treating chronic depression or TRD have been investigated. Treating depressed patients with comorbid psychiatric, personality, or medical disorders is a clinical challenge that requires effective multidisciplinary collaboration.

Key Words: comorbidity, chronic depression, treatment resistant depression, antidepressant medications, psychotropic drugs, psychotherapies, neuromodulation therapies, multidisciplinary collaboration

Introduction

Most depressions follow an episodic course, but about 20% of patients have symptoms that persist for 2 years or longer, referred to as chronic depression. A surprisingly large percentage of chronically depressed patients have never been treated or have received inadequate treatment (Kocsis et al., 2008). Despite apparently adequate antidepressant therapy, however, a significant proportion of depressed patients do not have a good treatment response. Treatment-resistant depression (TRD) generally is defined as the failure to achieve full remission following two or more sequential treatment trials using different antidepressant drugs at adequate doses for an adequate duration of time (Fava, 2003). A significant minority of depressed patients (about 20%–30%) have severe chronic TRD, characterized by a lack of response to multiple sequential trials of antidepressant drugs alone and various drug–drug and drug–psychotherapy combinations.

As described in the other chapters throughout this book, major depression and other depressive disorders are commonly associated with various comorbid psychiatric, personality, and medical disorders. Compared with patients with episodic depression, patients with chronic depression or TRD have higher rates of comorbidity, as well as more persistent social and vocational disability, an increased risk of suicide, greater medical morbidity and mortality, and greater health care utilization and costs (Berlim & Turecki, 2007; Blanco et al., 2010; Fagiolini & Kupfer, 2003; Fekadu et al., 2009; Holzel, Harter, Reese, & Kriston, 2011; Howland, 1993a; Rosenstein, Soleymani, & Cai, 2004).

In this chapter, I will first provide an overview of available antidepressant medications and other

drugs commonly used in combination with antidepressants, highlighting the potential relevance of associated comorbidity for the selection of various medications. I will then review psychotherapy and neuromodulation therapies for depression, with an emphasis on their use for treating chronic depression or TRD, where comorbidity is a common occurrence. I will finish with a discussion of clinical guidelines for practitioners.

Antidepressant Drugs

Antidepressant drugs are classified according to their chemical structure or mechanism of action: tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and atypical antidepressants (a disparate group of drugs not related to other classes).

TCA Drugs

The TCAs, so-called because of their three-ring cyclic chemical structure, were discovered in the late 1950s and commonly used until the late 1980s (Sartorius et al., 2007). The TCAs include imipramine, desipramine, amitriptyline, nortriptyline, doxepin, trimipramine, protriptyline, and clomipramine. Amoxapine and maprotiline are classified among the TCAs, but they actually have a four-ring "tetracyclic" chemical structure. The TCAs are effective for anxiety, especially generalized anxiety disorder (GAD) and panic disorder (PD). With the exception of clomipramine, an approved treatment for obsessive-compulsive disorder (OCD), the TCAs are not particularly effective for OCD. The antidepressant and antianxiety effects of TCAs are related to their reuptake inhibition of the neurotransmitters norepinephrine (NE) and serotonin (5-HT). The superior effectiveness of clomipramine compared with other TCAs for treating OCD is due to its relatively greater potency on 5-HT activity in the central nervous system (CNS). The TCAs block 5-HT_2 receptors (a 5-HT receptor subtype), contributing to their antidepressant, antianxiety, and positive sleep effects. They also block cholinergic, histamine, and α-adrenergic receptors, accounting for such adverse effects as dry mouth, constipation, sedation, weight gain, and hypotension. Other uses of TCAs include the treatment of insomnia, chronic pain, migraine and other headaches, and attention-deficit disorder (ADD). In depressed cancer patients, TCAs can be beneficial for pain, appetite, and insomnia. Amoxapine, a derivative of the antipsychotic drug loxapine, weakly blocks dopamine (DA) receptors and has been used to treat psychotic depression. Due to anticholinergic effects, which are associated with adverse cognitive effects, TCAs are typically avoided in patients with dementia. They have cardiotoxic effects and can lower the seizure threshold, so they should be avoided in patients with cardiovascular disease or epilepsy. TCAs are not preferred in elderly patients because of their overall side effect profile. Although TCAs are used infrequently in contemporary clinical practice, they are effective for patients with very severe depression and for TRD.

MAOI Antidepressant Drugs

The MAOIs, also discovered in the late 1950s, inhibit MAO enzyme activity (Sartorius et al., 2007). In the CNS, liver, and gut, MAO metabolizes various "amine" chemical entities. Important "amines" include the indoleamine 5-HT and the catecholamines NE and DA. By inhibiting MAO activity, the availability of neurotransmitters is increased, contributing to the antidepressant properties of MAOI drugs. The older MAOI drugs are phenelzine, isocarboxazid, and tranylcypromine. Although used even less frequently than TCAs, MAOIs are considered especially effective for PD, agoraphobia, and social anxiety disorder (SAD). MAOIs are effective for atypical, anxious, bipolar, and treatment-resistant forms of depression, with some evidence suggesting they might be more effective than TCAs for these depression subtypes.

A significant concern using MAOI drugs is the risk of dietary and drug–drug interactions. An adequate dietary intake of the amino acid tyrosine, found in proteins, is necessary for synthesizing catecholamines (i.e., epinephrine, NE, and DA). When tyrosine-containing foods are aged, fermented, ripened, or spoiled, tyrosine is converted to the "amine" tyramine. Tyramine is metabolized by MAO in the gut and liver and very little circulates in the body. Severe hypertension can occur with an MAOI when large amounts of tyramine-containing foods are ingested. MAOI-treated patients are susceptible to severe drug–drug interactions with other antidepressants, anticonvulsants, opioid analgesics, cough suppressants, muscle relaxants, decongestants, weight-loss products, stimulants, and herbal/dietary supplements.

Selegiline is a more selective inhibitor of MAO (Howland, 2006a). Low-dose selegiline increases the availability of DA, and for this reason it is used to treat Parkinson's disease. At low doses, it does not

have the same risk of dietary or drug–drug interactions as older MAOI drugs but does not have significant antidepressant effects. At higher doses, selegiline loses its selectivity and is an effective antidepressant but has similar dietary and drug interactions as older MAOIs. To overcome the problems associated with using selegiline at higher antidepressant doses, a transdermal (skin patch) formulation of selegiline was developed (Howland, 2006b). Transdermal selegiline is approved for the treatment of depression and is less likely to be associated with adverse dietary and drug–drug interactions, but it has not been investigated for conditions other than depression.

SSRI Antidepressant Drugs

The SSRI drugs were first introduced in the late 1980s and are the most commonly used antidepressant drugs (Sartorius et al., 2007). The SSRI drugs fluvoxamine, fluoxetine, paroxetine, sertraline, citalopram, and escitalopram are effective for the treatment of anxiety, and they each have various approved indications for specific anxiety disorders, including GAD, PD, SAD, posttraumatic stress disorder (PTSD), and OCD. These drugs also are used for the treatment of premenstrual dysphoric disorder (fluoxetine, paroxetine, and sertraline have approvals for this indication), eating disorders (fluoxetine is approved for bulimia nervosa), substance use disorders, and migraine headache. With the exception of citalopram and escitalopram (which are enantiomer-related drugs), the SSRI drugs are not chemically similar, but they have a common mechanism of action (potent and relatively selective inhibition of 5-HT reuptake). Similar to clomipramine, the potent 5-HT reuptake inhibitory effect of SSRI drugs makes them more effective than other antidepressants for OCD.

SSRIs do not have significant adverse cardiac effects and are much safer than TCAs and MAOIs in overdose. Rarely, SSRI drugs can be associated with parkinsonian symptoms and should be used carefully in patients with Parkinson's disease. Hyponatremia (low serum sodium) is a rare but potentially serious complication related to the use of SSRI drugs. This may be more common in elderly patients, especially when used together with other drugs associated with hyponatremia. SSRI drugs have been associated with an aspirin-like antiplatelet effect (i.e., bruising and bleeding). This sometimes includes serious upper gastrointestinal bleeding, especially in elderly patients taking nonsteroidal anti-inflammatory drugs or other blood-thinning medications. However, the antiplatelet effect of SSRI drugs may also have positive cardiovascular benefits in depressed patients with comorbid cardiac disease.

SNRI Antidepressant Drugs

The primary mechanism of action of SNRI drugs is 5-HT and NE reuptake inhibition (Sartorius et al., 2007). Venlafaxine, approved for depression and the anxiety disorders SAD, GAD, and PD, is used for other anxiety disorders, ADD, substance use disorders, chronic pain conditions, headaches, and perimenopausal hot flashes. Desvenlafaxine, the major active metabolite of venlafaxine, is approved for depression, but it has not been studied for anxiety or other disorders. The SNRI duloxetine has structural similarities to the SSRI fluoxetine; is approved for depression, diabetic peripheral neuropathy, fibromyalgia, and GAD; and is used for urinary incontinence. The use of SNRI drugs has increased in recent years. Their tolerability and safety profile are not significantly different than SSRI drugs, including their cardiac safety.

Atypical Antidepressant Drugs

Bupropion is an aminoketone antidepressant whose mechanism of action is uncertain, although it may enhance the effects of NE and DA (Sartorius et al., 2007). It is approved for depression, seasonal affective disorder, and smoking cessation and is commonly used for treating substance use disorders. Bupropion is not associated with weight gain, sedation, or sexual dysfunction, and it is a good choice for patients with comorbid obesity, hypersomnia, chronic fatigue, or sexual dysfunction. It is often combined with SSRI and SNRI drugs to treat adverse sexual effects or to augment their antidepressant effects. It is sometimes used as an alternative to stimulant drugs for the treatment of ADD. Using higher than recommended doses is associated with an increased risk of seizures, which have been observed when it was used in patients with bulimia. It should be avoided in patients with eating disorders or epilepsy.

Trazodone is a phenylpiperazine compound that has weak effects on neurotransmitter reuptake, but it blocks 5-HT_2 receptors and α_1-adrenergic receptors (Sartorius et al., 2007). Side effects limit its use as an antidepressant. Because trazodone is sedating, it is used almost exclusively in low doses for treating insomnia, often combined with other antidepressants. It has antianxiety effects at lower doses, but higher doses are needed to treat depression

effectively. A rare serious adverse effect associated with high doses, related to α_1-blocking effect, is priapism (persistent erection). Higher antidepressant doses should be used only in women.

Nefazodone is structurally related to trazodone. Its primary mechanism of action is blockade of 5-HT_2 receptors (Sartorius et al., 2007). It has less potent effects on α_1-receptors and very weak NE and 5-HT reuptake inhibition. Compared with SSRIs and TCAs, it is not associated with sexual dysfunction or weight gain. Compared with trazodone, it is not as sedating and does not cause priapism, but it is beneficial for comorbid insomnia and anxiety.

Mirtazapine is a piperazinoazepine antidepressant with a complex mechanism of action (Howland, 2008). It blocks presynaptic α_2-adrenergic receptors and postsynaptic 5-HT_2 and 5-HT_3 serotonin receptors, resulting in a net effect of increasing 5-HT and NE transmission. Mirtazapine potently blocks histamine receptors, contributing to its most prominent adverse effects (i.e., sedation and weight gain). Because of mirtazapine's complex pharmacological effects, it is often used in combination with other antidepressants to enhance treatment response. It is less likely to cause nausea, headache and sexual dysfunction than do SSRIs and SNRIs. In depressed cancer patients, mirtazapine attenuates nausea associated with chemotherapy, and it can improve appetite and sleep. Mirtazapine improves negative symptoms in schizophrenia and may be a good choice for treating depression in patients with schizophrenia.

Vilazodone is a phenylpiperazine chemical derivative (having pharmacological similarities to trazodone and nefazodone) that has dual activity as a 5-HT reuptake inhibitor and 5-HT_{1A} receptor agonist (Howland, 2011). Vilazodone may be effective for the treatment of anxiety disorders, but it has not been studied for these conditions. With the exception of possibly fewer adverse sexual effects, vilazodone has a tolerability profile similar to SSRI drugs.

Combination and Augmentation Strategies for Treating Depression

Combination therapy refers to the combined use of two antidepressant drugs, whereas augmentation therapy refers to the addition of a second nonantidepressant agent to an antidepressant drug (Fava & Rush, 2006). Adding a second medication to the primary antidepressant is usually done to improve the overall antidepressant response, but can be used to target other associated symptoms (e.g., anxiety or insomnia), comorbid conditions (e.g., substance abuse or ADD), or side effects (e.g., sexual dysfunction or weight gain). Combination and augmentation strategies are commonly used for TRD patients who have not responded to sequential monotherapy trials using single antidepressants from several different classes.

With the exception of MAOI drugs, combining antidepressants usually can be safely done. The effectiveness of various antidepressant combinations for TRD has not been well studied (Fava & Rush, 2006). Combinations of SSRIs and TCAs, and other antidepressant combinations, have been described, but they are mostly small anecdotal reports or uncontrolled studies. The most common approaches involve combining SSRI drugs with bupropion or mirtazapine.

Bupropion combinations are popular, but their efficacy for TRD has not been extensively studied (Zisook, Rush, Haight, Clines, & Rockett, 2006). In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, the efficacy and tolerability of various antidepressant therapies were evaluated in 2876 depressed patients through four sequential treatment steps (Rush et al., 2006). Because STAR*D was intended to be a "real world" clinical trial, 60% of subjects were recruited from psychiatric clinics and 40% of subjects were recruited from medical sites. Comorbid psychiatric, personality, and general medical conditions and concurrent use of other medications did not exclude patients from the study. The age range was 18–75 years, and 25% were older than 50 years. In Level 1 of STAR*D, all patients were treated with the SSRI citalopram (Trivedi et al., 2006b). In the augmentation arm of Level 2, citalopram nonremitters were randomized to receive augmentation with bupropion or buspirone (Trivedi et al., 2006a). The bupropion and buspirone groups had similar remission and response rates, but bupropion had a significantly lower dropout rate due to intolerance.

Mirtazapine combinations are another approach for TRD. In a randomized controlled trial, patients who did not respond to monotherapy with an SSRI, venlafaxine, or bupropion continued to take the ineffective drug and were randomized to receive a combination using either mirtazapine or placebo (Carpenter, Yasmin, & Price, 2002). Mirtazapine combination response rate (63.6%) was significantly better than placebo combination (20.0%). When nine placebo nonresponders were treated openly with mirtazapine at the end of the study, five patients (55.5%) remitted. In the last level of STAR*D, nonremitters after

the first three levels were randomly assigned to switch to the MAOI drug tranylcypromine or to a venlafaxine-mirtazapine combination (McGrath et al., 2006). Tranylcypromine remission rates were lower than for the venlafaxine-mirtazapine combination, although the difference was not statistically significant. Tranylcypromine was associated with significantly less symptom reduction and greater attrition due to intolerance than was the combination.

Augmentation of Antidepressants With Other Drugs

Lithium

Lithium is an approved mood-stabilizer treatment for bipolar disorder and is effective for treating bipolar depression. Patients with recurrent mood disorders (bipolar disorder or recurrent major depression) who take lithium are significantly less likely to make suicide attempts or to complete suicide. A randomized study comparing the anti-suicide effects of lithium versus the anticonvulsant mood-stabilizer valproate in patients with bipolar disorder with previous suicide attempts found no difference between the drugs on suicide attempts (Oquendo et al., 2011). Based on randomized placebo-controlled studies, lithium is the most extensively studied and best established augmentation strategy for TRD, including elderly patients (Cooper et al., 2011; Crossley & Bauer, 2007). In the augmentation arm of Level 3 of STAR*D, non-remitters after two levels were randomly assigned to augmentation with lithium or thyroid hormone (triiodothyronine [T_3]) (Nierenberg et al., 2006). Lithium remission rates were lower than for T_3, but the difference was not statistically significant. Lithium had more side effects, and more lithium patients left treatment because of side effects. Because lithium is eliminated through the kidneys, patients with impaired kidney function or patients taking drugs that affect kidney functioning should not take lithium.

Anticonvulsant Drugs

Anticonvulsant drugs are approved for the treatment of seizure disorders, many are used as mood-stabilizing drugs for treating bipolar disorder, and they are often used for anxiety, substance use disorders, impulse control disorders, chronic pain, migraine and other headache disorders, and mood instability in personality disorders. Valproate, carbamazepine, lamotrigine, gabapentin, and topiramate are used most commonly in psychiatric practice.

Valproate (valproate, valproic acid, and divalproex sodium are different formulations of the same chemical compound) is the most frequently used anticonvulsant in psychiatric practice (Haddad, Das, Ashfaq, & Wieck, 2009). It is approved for the treatment of bipolar disorder and migraine headaches, and has been used in the treatment of anxiety disorders, behavioral dyscontrol syndromes, alcohol and benzodiazepine withdrawal, alcohol dependence, and schizophrenia. Valproate is potentially toxic to the liver, but this effect is rare in adults compared with in children, and the drug has been used safely in alcohol-dependent patients.

Carbamazepine is approved for the treatment of bipolar disorder and trigeminal neuralgia, and has been used for anxiety disorders, behavioral dyscontrol syndromes, neuropathic pain, and alcohol and benzodiazepine withdrawal. Carbamazapine has a central TCA-like chemical structure and has significant antidepressant effects in unipolar depression (Zhang et al., 2008). In an open-label randomized study, carbamazepine and lithium augmentation were similarly effective for TRD (Rybakowski, Suwalska, & Chlopocka-Wozniak, 1999). Carbamazepine potently induces metabolic enzymes in the liver, which can decrease serum levels of other drugs and lessen their clinical effects. Oxcarbazepine is a chemical analogue of carbamazepine, but it is better tolerated and less likely to induce metabolic enzymes in the liver. Though sometimes used in psychiatric practice as an alternative to carbamazepine, its effectiveness has not been established. It is not currently approved for any use in psychiatry.

Lamotrigine is an approved treatment for bipolar disorder, but may have relatively better antidepressant effects than other anticonvulsant drugs (Ernst & Goldberg, 2003). Open-label and controlled studies have not found consistent benefit for lamotrigine in unipolar depression, although comorbid anxiety symptoms and symptoms associated with borderline personality are improved (Zavodnick & Ali, 2012). Open-label studies found lamotrigine effective for unipolar TRD. A small placebo-controlled study did not demonstrate significant benefit for lamotrigine augmentation in TRD on the primary outcome measure, but it was significantly more effective than placebo on several secondary outcome measures. In an open-label randomized study, lamotrigine and lithium augmentation were similarly effective for unipolar TRD.

Gabapentin, an approved treatment for postherpetic neuralgia, did not have significant efficacy for

bipolar disorder in controlled studies (Fountoulakis et al., 2012) but may be beneficial for anxiety, insomnia, perimenopausal hot flashes, headaches, neuropathic pain syndromes, and surgical pain (Megna, Iqbal, & Aneja, 2003). Gabapentin is commonly used together with antidepressants for depressed patients with these comorbid conditions.

Topiramate also did not have significant benefit for bipolar disorder in controlled studies (Kushner, Khan, Lane, & Olson, 2006) but is approved for treating migraine headaches and is effective for neuropathic pain, behavioral dyscontrol, alcohol dependence, bulimia, binge-eating, and obesity. Topiramate can cause weight loss, and it is used to treat weight gain associated with other psychotropic drugs (McIntyre et al., 2012).

Several other anticonvulsant drugs are not frequently used but have potential roles in treating depression comorbidities (Grunze, 2008). Zonisamide is not used for treating bipolar disorder but is effective for migraine headache, binge-eating, and obesity. Similar to topiramate, it causes weight loss and may be used to manage psychotropic drug–related weight gain. Controlled studies of tiagabine have demonstrated its efficacy in GAD, but it is not effective for mood disorders. Preliminary studies of levetiracetam suggest some benefit in the treatment of bipolar disorder, anxiety, and movement disorders. Pregabalin is approved for diabetic neuropathy, neuropathic pain, and fibromyalgia and has been used to treat anxiety symptoms.

Second-Generation Antipsychotic Drugs

The pharmacology of second-generation antipsychotic (SGA) drugs (atypical antipsychotics) is more complex than first-generation (typical) antipsychotic drugs (FGAs). Because of their dopamine DA-2 receptor–blocking effects, the SGAs are classified as antipsychotic drugs and all are approved for schizophrenia. Compared with FGAs, the SGAs have significantly greater effects on blocking 5-HT_2 receptors and have effects on other neurotransmitters and their receptors (Shelton & Papakostas, 2008). Similar to lithium and some anticonvulsant drugs, SGAs are effective for bipolar mania and bipolar depression. Nearly all have approved indications for bipolar disorder, and they are often used for impulse control disorders and mood instability in personality disorders. Many SGAs have antidepressant effects and are used for treating psychotic depression. Other uses of some SGAs include Tourette syndrome and other tic disorders and to augment SSRIs for treating OCD.

With the exception of lithium, SGA drugs are now the best studied augmentation agents with antidepressants for unipolar TRD in placebo-controlled trials (Shelton & Papakostas, 2008). Aripiprazole is approved for bipolar disorder and as an add-on therapy (together with another antidepressant drug) for unipolar TRD (Berman et al., 2009). Quetiapine is approved for bipolar mania, bipolar depression, and as an add-on therapy with another antidepressant for unipolar TRD (Bauer et al., 2009). It is often used in low doses for anxiety and insomnia, but sedation and weight gain are a problem. Olanzapine is approved for bipolar disorder, is effective for bipolar depression, and is sometimes used in low doses for anxiety and insomnia (although weight gain and sedation limits this use). The proprietary combination of fluoxetine and olanzapine (olanzapine-fluoxetine combination) is approved for bipolar depression and unipolar TRD (Trivedi et al., 2009). Risperidone, approved for bipolar disorder, is effective for unipolar TRD, but it is not approved for this indication (Mahmoud et al., 2007). Ziprasidone, approved for bipolar disorder, has not been well studied for unipolar TRD (Rosa et al., 2008).

Buspirone

Buspirone, an azapirone nonbenzodiazepine drug indicated for the treatment of GAD, is a partial 5-HT_{1A} receptor agonist, modulating 5-HT release. It has antidepressant properties at high doses (up to 60–90 mg/day) and may be beneficial for smoking cessation. Buspirone is often combined with antidepressant drugs to treat adverse sexual effects or to augment their antidepressant effects. Controlled studies have found buspirone augmentation to be effective in TRD (Appelberg et al., 2001). As described previously, buspirone was somewhat less effective and less well tolerated than bupropion in the augmentation arm of Level 2 in STAR*D (Trivedi et al., 2006a).

Stimulant Drugs

The two stimulant drug classes are methylphenidate compounds and amphetamine compounds. Methylphenidate and amphetamine formulations are approved for ADD and narcolepsy and are used for daytime somnolence in patients with sleep apnea. Before the advent of conventional antidepressants, stimulants were commonly used to treat depression (Howland, 2012). In contemporary practice, they are used for treating depression in elderly patients and medically ill patients. Stimulants are used to increase alertness, cognition, motivation, and

motor performance in patients with brain injuries and other neurological conditions. They are added to antidepressants to augment their clinical effects and to treat such adverse effects as fatigue, apathy, and sexual dysfunction. They can be used to treat obesity, including psychotropic drug-induced weight gain. An open-label study found that adding dextroamphetamine to MAOIs was safe and effective for patients with TRD. However, several recent placebo-controlled studies did not find a significant antidepressant benefit when methylphenidate was used to augment antidepressant medication and a placebo-controlled study did not find methylphenidate effective for treating antidepressant-associated sexual dysfunction.

Atomoxetine

Atomoxetine is a selective NE reuptake inhibitor drug that has weak antidepressant effects and is not approved for depression but is approved for the treatment of ADD. A placebo-controlled study of atomoxetine augmentation for TRD found no benefit, although the drug might be useful for treating fatigue associated with depression (Howland, 2012).

Modafinil

Modafinil has a stimulating effect in the CNS unlike that of methylphenidate or amphetamine. It is approved for narcolepsy and excessive daytime sleepiness associated with sleep apnea, has been used as alternative treatment for ADD, may be beneficial for helping with psychotropic drug-induced weight gain, and is sometimes added to antidepressants (typically SSRIs) to augment their clinical effect and to treat certain adverse effects (e.g., apathy, fatigue, and sexual dysfunction). A pooled analysis of two placebo-controlled augmentation studies found it modestly effective for improving depression, sleepiness, and fatigue (Howland, 2012). A placebo-controlled augmentation study in patients with bipolar depression demonstrated significant antidepressant benefits. A small open-label study suggested possible efficacy for modafinil in seasonal affective disorder.

Benzodiazepine and Sedative-Hypnotic Drugs

The amino acid γ-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the CNS. GABA receptor systems are the target of a wide range of drugs, including antianxiety, sedative-hypnotic, general anesthetic, and anticonvulsant drugs. GABA modulates the activity of the neurotransmitters 5-HT, NE, and DA. Reduced plasma, spinal fluid, and CNS GABA levels are found in depression (Krystal et al., 2002).

Benzodiazepine receptor agonist drugs (BzRAs) bind to GABA receptors in the CNS. The two BzRA drug classes are referred to as benzodiazepine and nonbenzodiazepine drugs (Becker & Sattar, 2009). Eight benzodiazepine drugs are approved for anxiety: alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, halazepam, lorazepam, and oxazepam. They are commonly used for insomnia and can be used to detoxify alcohol-dependent patients. Clonazepam is used for restless legs syndrome, which often is associated with depression. Five benzodiazepine drugs are approved specifically for the short-term treatment of insomnia: estazolam, flurazepam, quazepam, temazepam, and triazolam. They are usually not used for treating anxiety. Three nonbenzodiazepine BzRA drugs are approved for insomnia: zolpidem, zaleplon, and eszopiclone. They are chemically unrelated to the benzodiazepines and have hypnotic effects without significant antianxiety or anticonvulsant effects. The nonbenzodiazepine drugs are better tolerated than benzodiazepines, less prone to daytime effects, have a lower abuse liability, and have been better studied in elderly patients. Ramelteon, a synthetic analog of the pineal gland hormone melatonin (Rajaratnam, Cohen, & Rogers, 2009), is a melatonin receptor agonist drug approved for the treatment of insomnia. It is structurally unrelated to BzRA drugs and does not bind to GABA receptors.

Sleep disturbances are common in depressed patients. Insomnia increases the risk of new-onset depression as well as the risk of recurrence of depression (Manber & Chambers, 2009). Disturbed sleep is associated with a less than optimal response to antidepressant medication. Several studies have found that the co-administration of various benzodiazepine drugs or zolpidem improve the sleep of depressed patients without impairing the antidepressant response (Jindal & Thase, 2004). A placebo-controlled study found that augmentation of fluoxetine with eszopiclone not only improved sleep but also led to a significantly greater antidepressant remission rate (Fava et al., 2006). The benzodiazepine drugs alprazolam and clonazepam have been demonstrated to have antidepressant effects (Morishita, 2009; Warner, Peabody, Whiteford, & Hollister, 1988). Hence, the judicious use of benzodiazepines or other sedative-hypnotics can be beneficial for treating insomnia and enhancing the effectiveness of antidepressants.

Glutamate-Modulating Drugs

Glutamate is the major excitatory amino acid neurotransmitter throughout the CNS and is important in many physiological processes, including neurotrophism (neuronal growth and maintenance), cognition (learning and memory), and neurodegeneration (neuronal damage or death). Glutamate systems have been implicated in mood and anxiety disorders, schizophrenia, substance abuse (e.g., alcohol and hallucinogens), and neurodegenerative disorders (e.g., stroke, traumatic brain injuries, and Alzheimer's disease) (Howland, 2007). One important type of glutamate receptor is the *N*-methyl-D-aspartate (NMDA) receptor. Memantine, a weakly binding NMDA receptor antagonist, is an approved treatment for Alzheimer's disease. It has been investigated in other cognitive and neurodegenerative disorders, and it may decrease alcohol craving and intake. A double-blind placebo-controlled study of patients with major depression did not show that memantine was effective and it has not been studied in TRD. Acamprosate attenuates the effect of glutamate, possibly by NMDA receptor antagonism similar to memantine, and is approved for the maintenance treatment of abstinence in alcohol abuse. It is not effective unless the patient has stopping drinking.

Histamine-Blocking Drugs

Histamine is a neurotransmitter that binds to H1 and H2 receptors in the CNS (Simons & Simons, 2011). Activation of H2 receptors in the stomach promotes acid secretion, and drugs that block this effect are used for the treatment of acid reflux. Activation of H1 receptors in the CNS promotes wakefulness and is involved in processes that regulate satiety (hunger) and cellular metabolism. Drugs blocking H1 receptors are associated with sedation and increased appetite. Diphenhydramine, hydroxyzine, promethazine, and cyproheptadine block H1 receptors and have mild anticholinergic effects. Cyproheptadine also strongly blocks 5-HT_2 receptors. Diphenhydramine is commonly used for treating insomnia, mild anxiety, and drug-induced parkinsonian effects. Hydroxyzine and promethazine are used mostly for insomnia and mild anxiety. Cyproheptadine has been used for insomnia. It also is used to promote appetite and weight gain in patient with anorexia nervosa and in patients taking appetite-suppressing drugs (e.g., stimulant drugs). Its 5-HT_2–blocking effects have been used to counter the adverse 5-HT effects of drugs (e.g., sexual dysfunction associated with SSRIs).

Opioid Receptor Drugs

The discovery of opioid receptors in the early 1970s led to the identification of endogenous opioid peptides (e.g., dynorphins, enkephalins, and endorphins). The effects of endogenous opioid peptides and exogenous opioid drugs (i.e., heroin, morphine, and others) are mediated by three major opioid receptor subtypes (μ-opioid, κ-opioid, and κ-opioid). Preclinical and clinical research has suggested that functional abnormalities in opioid systems may be involved in the pathophysiology of depression (Howland, 2010). Opioid drugs were often used to treat depression until the mid-1950s. Many nonopioid antidepressant drugs directly and indirectly affect opioid receptors. Improvement in mood has been observed in patients during treatment with cyclazocine, which is a mixed agonist/antagonist opioid drug not currently available, as well as during beta-endorphin infusions and with the use of a synthetic enkephalin analogue.

Buprenorphine, a synthetic opioid analgesic drug, is a partial μ-opioid receptor agonist and κ-opioid receptor antagonist. This mixed agonist/antagonist effect may produce less euphoria, with a lower liability for tolerance, dependence, and abuse compared with other opioid drugs. Buprenorphine has approved indications for analgesia, detoxification from opioid drug addictions, and for opioid dependence (Howland, 2010). In an open-label study, among 40 opioid addicts treated as outpatients with buprenorphine for a month, depressive symptoms significantly decreased in the 19 patients who were depressed at intake. Rapid improvement in mood with the use of buprenorphine was observed in 7 of 10 nonopioid abusing patients with TRD. Six patients with TRD treated with buprenorphine all improved. A double-blind, placebo-controlled cross-over study of buprenorphine demonstrated a significant improvement in depression in four patients and a slight to moderate response in the remaining nine patients.

Naltrexone is a pure opioid receptor antagonist drug that can be used for rapid detoxification from opioid drug addictions and has approved indications for opioid dependence and alcohol dependence (Howland, 2010). Similar to SSRIs, naltrexone was effective in alleviating symptoms of premenstrual syndrome in a double-blind placebo-controlled study involving 20 women.

Dopamine-Releasing and Dopamine-Agonist Drugs

Dopamine-releasing and dopamine-agonist drugs are sometimes used to augment antidepressants

and to relieve side effects such as apathy and sexual dysfunction (Howland, 2012). Amantadine is an approved treatment for influenza, Parkinson's disease, and drug-induced parkinsonian side effects. It increases DA activity by facilitating the release of DA and possibly blocking the reuptake of DA. One open-label study found it effective in augmenting antidepressant drugs in TRD. A nonrandomized parallel-group study found that imipramine plus amantadine was more effective than imipramine alone for patients with TRD. Bromocriptine is a DA receptor agonist that is approved for the treatment of hyperprolactinemia and Parkinson's disease. It is sometimes used to treat hyperprolactinemia and parkinsonian effects associated with antipsychotic drugs. A small open-label study found that adding bromocriptine to TCA drugs was effective for TRD. Pramipexole and ropinirole are DA receptor agonist drugs approved for treating Parkinson's disease and restless legs syndrome. A controlled study comparing pramipexole, fluoxetine, and placebo for major depression demonstrated that both active drugs were more effective than placebo. Two small placebo-controlled studies also found significant benefit for pramipexole for bipolar depression (Goldberg, Burdick, & Endick, 2004; Zarate et al., 2004). Open-label studies of pramipexole and ropinerole also suggested that they may be effective when used to augment antidepressant medication in TRD.

Thyroid Hormones

Clinical hypothyroidism often is associated with depression. Most studies of depressed patients have found low rates of hypothyroidism, but subclinical hypothyroidism may be relatively more common in chronic depression or TRD, requiring combined treatment with antidepressant drugs and thyroid hormone augmentation (Howland, 1993b). Thyroid augmentation has been studied in TCA nonresponders and SSRI nonresponders (Joffe, Singer, Levitt, & MacDonald, 1993; Nierenberg et al., 2006). Thyroid augmentation may be more effective in women, perhaps because of their higher risk for thyroid disease (Whybrow, 1995). Thyroid hormone augmentation has been less well studied than lithium augmentation or SGA augmentation but better studied than other combination and augmentation strategies. In a placebo-controlled comparison, T_3 and lithium augmentation were similarly effective for TCA TRD (Joffe et al., 1993). However, as described previously, T_3 was somewhat more effective and better tolerated than lithium in the Level 3 augmentation arm of the STAR*D study (Nierenberg et al., 2006).

Sex Steroid Hormones

Sex steroid hormones act on specific receptors in the brain and affect neuronal function and neurotransmission (Deecher, Andree, Sloan, & Schechter, 2008). Women are especially vulnerable to mood disturbances during premenstrual, postpartum, and perimenopausal periods. Mood disturbances also may be associated with decreased steroid hormone levels in men (Shores, Kivlahan, Sadak, & Matsumoto, 2009). Estrogen may improve mild mood symptoms in perimenopausal women (Epperson, Wisner, & Yamamoto, 1999), but there is less consistent evidence that estrogen or estradiol is effective alone for major depression (Morgan, Cook, Rapkin, & Leuchter, 2005; Morrison et al., 2004). Some studies, but not all, have found that estrogen may augment the effects of antidepressant drugs (Amsterdam et al., 1999; Morgan et al., 2005; Schneider et al., 1997; Shapira et al., 1985). A small placebo-controlled study found that estrogen augmentation was effective for perimenopausal women with TRD (Morgan et al., 2005). There is inconsistent evidence for antidepressant effects of testosterone in men. Several small placebo-controlled studies of testosterone augmentation in men with TRD had mixed results (Kanayama, Amiaz, Seidman, & Pope, 2007). A placebo-controlled study found that testosterone replacement was effective in older hypogonadal men with dysthymia or minor depression (Shores et al., 2009). The adrenal steroid hormone dehydroepiandrosterone (DHEA), a precursor to testosterone and estrogen, may have significant antidepressant effects (Schmidt et al., 2005; Wolkowitz et al., 1999). A small placebo-controlled study suggested benefit with DHEA augmentation for TRD (Wolkowitz et al., 1999).

Psychotherapy for Chronic Depression and Treatment-Resistant Depression

Compared with traditional forms of psychotherapy, depression-focused psychotherapies have been better studied in clinical trials, and some studies have shown them to be as effective as pharmacotherapy for the treatment of depressed outpatients (Parikh et al., 2012).

Intensive short-term dynamic psychotherapy (ISTDP) was developed as an emotion-focused process that helps to overcome problems in regulating complex feelings associated with depression. Meta-analyses suggest that brief dynamic therapy

methods are effective in treating general psychiatric symptoms and for providing added benefits to medication in major depression (Leichsenring, Rabung, & Leibing, 2004; Pampallona, Bollini, & Tibaldi, 2004). A pilot study describes the use of ISTDP for TRD (Abbass, 2006). Interpersonal psychotherapy (IPT) is a time-limited form of psychotherapy that focuses on difficulties in the patient's intimate and vocational relationships. IPT is an effective treatment for depression (Parikh et al., 2012). A preliminary study described the effects of combining IPT and mirtazapine for TRD (Martin, Martin, & Hildreth, 2007). Various behavioral therapy (BT) approaches have been developed for the treatment of depression, such as activity scheduling, self-control techniques, and social skills training. Some controlled studies have found BT to be effective among outpatients with depression (Parikh et al., 2012). A case report described the use of BT in a patient with chronic TRD (Bottonari, Roberts, Thomas, & Read, 2008). Cognitive-behavioral therapy (CBT) is a time-limited form of psychotherapy based on the theory that depression is invariably associated with automatic negative thoughts about oneself, the world, and the future. CBT is the best studied form of psychotherapy for depression, including chronic depression and TRD (Eisendrath et al., 2008; Parikh et al., 2012; Wiles et al., 2008). Some studies have found CBT to be as effective as antidepressant medications (Hollon et al., 1992).

Combining pharmacotherapy and psychotherapy is often recommended in clinical practice, but there is only modest evidence that the combination is superior to either modality alone for uncomplicated depressions. A meta-analysis of controlled trials comparing pharmacotherapy alone to combination pharmacotherapy and psychotherapy found a small effect in favor of combination treatment (Cuijpers, Dekker, Hollon, & Andersson, 2009). Interestingly, the dropout rate was significantly lower in the combination group compared with the pharmacotherapy alone group, suggesting an important added benefit for enhancing treatment adherence. It is conceivable that depressed patients with comorbidity, who are more likely to have problems with treatment adherence, may benefit from combination therapy. Combining psychotherapy and pharmacotherapy might be preferred for managing complicated depressions such as chronic depression or TRD (Thase, Friedman, & Howland, 2001), but there is mixed evidence to support this (Trivedi, Nieuwsma, & Williams, 2010; von Wolff, Hölzel, Westphal, Härter, & Kriston, 2012).

Cognitive behavioral analysis system of psychotherapy (CBASP) is a modified form of CBT that incorporates some principles of IPT. In a large study of 681 patients with chronic depression, CBASP and nefazodone were similarly effective, but the combination of CBASP and nefazodone was significantly superior to each treatment alone (Keller et al., 2000). Patients not responding adequately to nefazodone or to CBASP initially had better outcomes when they were crossed over to the alternative treatment (Schatzberg et al., 2005).

In Level 2 of STAR*D, CBT was compared with medication augmentation and switch strategies for 304 citalopram nonremitters (Thase et al., 2007). The 304 patients were randomly assigned to augmentation (citalopram plus CBT or medication) or to switch (to CBT or another antidepressant). Patients who received CBT (either alone or combined with citalopram) had similar response and remission rates compared with those assigned to medication only. For patients who continued on citalopram, medication augmentation resulted in significantly more rapid remission than augmentation with CBT. Among those who discontinued citalopram (switching to CBT or medication), there were no significant differences in outcome, although patients who switched to a different antidepressant reported significantly more side effects than patients who received CBT alone.

In the Research Evaluating the Value of Augmenting Medication with Psychotherapy (REVAMP) study, adding psychotherapy to a medication change versus changing medication alone in chronic depressions with a partial or nonresponse to an initial antidepressant was evaluated in two phases (Trivedi et al., 2008). In Phase 1, 808 patients received an antidepressant selected according to a treatment algorithm based on their prior treatment history. At the beginning of Phase 2, 491 Phase 1 antidepressant nonresponders were switched to the next medication in the algorithm and randomized to receive supportive psychotherapy, CBASP, or pharmacotherapy alone. At the beginning of Phase 2, Phase 1 partial responders have their initial antidepressant augmented by adding a second medication and also are randomized to receive supportive therapy, CBASP, or pharmacotherapy alone. Patients who achieved remission during Phase 1 maintained their medication and were monitored during Phase 2. At the end of Phase 2, there were no significant differences in outcome for the three treatment groups (Kocsis et al., 2009).

Various psychotherapeutic approaches to treating anxiety disorders, substance use disorders,

personality disorders, and ADD have been described, but there is very little empirical evidence to evaluate whether combining these psychotherapies with pharmacotherapy is necessarily or especially effective for depressive disorders with any of these comorbidities (Beaulieu et al., 2012; Bond et al., 2012; Rosenbluth, MacQueen, McIntyre, Beaulieu, & Schaffer, 2012; Schaffer et al., 2012).

Neuromodulation Therapies for Chronic Treatment-Resistant Depression

Electroconvulsive Therapy for Depression

The oldest form of neuromodulation is electroconvulsive therapy (ECT), which involves the passage of a brief electrical current through the brain to induce a generalized seizure lasting about 30–90 seconds. A course of ECT consists of 6–12 treatments given three times weekly, although patients with TRD might require a greater number of treatments. ECT is highly effective for TRD (Sartorius et al., 2007), and it is generally considered safe for patients with comorbid medical conditions, including elderly patients and pregnant patients. The acute benefits of ECT are usually time-limited, and most patients should receive long-term continuation treatment with pharmacotherapy or with ECT. Patients who failed to respond to antidepressant medication prior to ECT have a higher risk of relapsing with pharmacotherapy after successful ECT and therefore should preferentially receive continuation treatment with ECT.

Transcranial Magnetic Stimulation for Depression

Transcranial magnetic stimulation (TMS) is a noninvasive method for causing focal nonelectrical stimulation of the brain without inducing seizures (Sartorius et al., 2007). A high-intensity electrical current is passed through an electromagnetic coil on the scalp. Rapidly turning the current on and off generates repetitive pulses of a magnetic field that is focused on particular cortical regions of the brain, depending on the therapeutic intent. Low-frequency stimulation inhibits neuronal excitability, whereas high-frequency stimulation is excitatory. Five TMS sessions are administered weekly for 4–6 weeks for treating depression. Sham-controlled studies have used high-frequency TMS focused on the left dorsolateral prefrontal cortex (DLPFC) because this area is hypofunctional in depression. Low-frequency TMS focused on the right prefrontal cortex also is effective (Fitzgerald et al., 2008). Controlled studies of TMS have found it effective in major depression, including TRD (George et al., 2010; Lam, Chan, Wilkins-Ho, & Yatham, 2008). TMS has been approved for the treatment of depressed patients who have not responded to a single antidepressant drug trial. Its effectiveness in severe chronic TRD may be relatively less compared with ECT (Lam et al., 2008). TMS would be a good treatment choice for patients with medication intolerance or with contraindications to using medication because of medical comorbidity.

Vagus Nerve Stimulation for Treatment-Resistant Depression

The vagus nerve (cranial nerve X) is a parasympathetic nerve composed of afferent (carrying sensory information from the viscera) and efferent (regulating parasympathetic autonomic function) fibers. Vagus nerve stimulation (VNS) involves the surgical implantation of a pacemaker-like programmable pulse generator that intermittently stimulates the left cervical vagus nerve (Howland, Shutt, Berman, Spotts, & Denko, 2011). VNS was approved for refractory epilepsy in 1997. VNS activates various limbic regions and affects neurotransmitters. Studies in epilepsy found that VNS had positive effects on mood symptoms. An open-label pilot study using VNS in a group of 60 subjects with chronic TRD reported a response rate of approximately 40%. During long-term follow-up of 59 patients from this study, 44% were responders (27% remitters) at 1 year (276) and 42% were responders (22% remitters) at 2 years.

A randomized double-blind study comparing active and sham VNS in 235 patients with chronic TRD did not find a statistically significant difference after 12 weeks of treatment (15% active response versus 10% sham) (Howland et al., 2011). At the end of the acute study, all patients received active VNS and were followed in a long-term study. A similar cohort of chronic TRD patients not receiving VNS were recruited and followed long term as a naturalistic control group. After 1-year follow-up, the VNS patients were significantly more likely to be improved (27% response; 16% remission) compared with the naturalistic control group (13% response; 7% remission). VNS was approved for chronic TRD in 2005, and it has shown benefit in open-label pilot studies for rapid-cycling bipolar disorder, treatment-resistant anxiety disorders, chronic headache, and Alzheimer's disease (Howland et al., 2011). The use of VNS is safe for patients with various comorbid conditions taking medical or psychotropic drugs.

Deep Brain Stimulation for Treatment-Resistant Depression

Brain imaging studies have delineated a cortical-limbic-thalamic-striatal neural circuit important for understanding depression and OCD (Kopell, Greenberg, & Rezai, 2004). Because ECT and other therapies are not always effective, the development of modern stereotactic neurosurgical methods (Binder & Iskandar, 2000) led to a renewed interest in neurosurgical interventions for severe chronic TRD. These procedures involve creating small selective lesions within particular brain regions, alleviating severe chronic TRD (Steele, Christmas, Eljamel, & Matthews, 2008) and treatment-resistant OCD (TR-OCD) (Greenberg et al., 2003) without causing complications that plagued the earlier "psychosurgery" procedures. Stereotactic methods are also used to implant electrodes in the brain. Electrical stimulation by these electrodes using pacemaker-like programmable devices can reversibly modulate brain function, by stimulating or inhibiting the activity of specific brain regions, without causing permanent lesions.

The most commonly used neurosurgical form of therapeutic brain stimulation is DBS (Pereira, Green, Nandi, & Aziz, 2007). This involves the placement of stimulation electrodes into deep subcortical regions of the brain. The particular electrode placement depends on the condition being treated. With electrode placement in various basal ganglia, deep brain stimulation (DBS) is an approved treatment for essential tremor, Parkinson's disease, and primary dystonia. DBS targeting the ventral capsule/ventral striatum (VC/VS) has been approved for severe chronic TR-OCD (Greenberg et al., 2006). Investigational studies of DBS have also been conducted for the treatment of refractory epilepsy, obesity, chronic pain, tardive dyskinesia, Tourette's syndrome, and other movement disorders.

At least five different brain regions have been identified as potential targets for DBS in depression (Hauptman, DeSalles, Espinoza, Sedrak, & Ishida, 2008), but uncontrolled open-label investigational studies of DBS for chronic TRD have focused on three regions: Subgenual anterior cingulate (Brodmann area 25; Cg25) (Holtzheimer et al., 2012; Kennedy et al., 2011; Lozano et al., 2012), VC/VS (Malone et al., 2009), and nucleus accumbens (Bewernick, Kayser, Sturm, & Schlaepfer, 2012). Subjects in these pilot studies were severely ill and impaired, had lengthy episodes of depression and did not respond to multiple trials of drug therapies and psychotherapy. Most had received ECT previously. Patients often had comorbid psychiatric and medical conditions that ordinarily might have excluded them from standard clinical trials. The number of subjects in each study ranged from 11 to 21 (total of 84 subjects across all studies). Nine of the 84 subjects had bipolar depression. The subjects were followed for 1–6 years. At the last follow-up across all studies, response rates ranged from 29% to 92% and remission rates ranged from 33% to 58%. The DBS surgical procedure and stimulation was relatively well tolerated. Infections occurred in a small number of subjects and one seizure reported. Transient adverse mood changes were noted in several patients. There were no adverse cognitive effects. The number of serious adverse effects was small, with no patient experiencing permanent deficits. Not surprising for this severely ill patient population, four subjects made suicide attempts and two completed suicide.

A major limitation of these studies is the lack of blinding and sham control. In the study by Holtzheimer et al. (2012), using DBS targeting Cg25, single-blind discontinuation was planned after 24 weeks of active DBS. Subjects were told they would be randomized to either active or sham stimulation, but all were to receive sham stimulation. In the three subjects who entered this phase, a depressive relapse occurred within the first 2 weeks of discontinuation and depressive symptoms did not improve immediately after stimulation was restarted. Because of safety concerns, this phase of the study was then eliminated for the remaining subjects. In a completed study (presented, but not yet published) of DBS targeting the VC/VS, 30 subjects with chronic TRD were randomized prospectively to receive active or sham stimulation during an initial 4-month double-blind phase followed by open-label active stimulation for all subjects (Dougherty et al., 2012). At the end of the blinded phase, the active stimulation response rate (20%) was not significantly superior to sham stimulation (14.3%). After 1-year follow-up with active stimulation, 6 of 29 subjects (21%) were considered treatment responders.

Clinical Guidelines for Practitioners

More than two dozen antidepressant medications and psychotherapies are currently available as options for treating depression. Choosing a treatment depends on several factors. Patient preference is most important. Patients who strongly favor medication or psychotherapy should be offered their preferred treatment. The selection of

psychotherapy should be based on the availability of an experienced psychotherapist able to provide an established therapy. Some patients may not necessarily tolerate or like a particular psychotherapy approach, just as some patients will not always tolerate medication, and switching to an alternative psychotherapy should be considered. Psychotherapy can be effectively administered by computer or telephone, improving access to psychotherapy services (Parikh et al., 2012). Switching to antidepressant medication should be considered for psychotherapy intolerance or nonresponse.

Medication selection depends on patient preference, past treatment history, family treatment history, clinical symptoms, expected side effect profile, and comorbid psychiatric, personality, or medical disorders. The type of comorbid condition(s) may suggest the use of a particular medication or combination of medications to enhance overall response, target residual symptoms, or manage adverse effects. This is especially true for Axis I psychiatric comorbidity. The similarity of Axis II personality disorder symptom clusters (i.e., Cluster A psychotic-like symptoms, Cluster B mood instability symptoms, and Cluster C anxiety-related symptoms) to the symptoms of some Axis I disorders suggests that similar medication interventions might be considered for some depressed patients with comorbid personality disorders (Rosenbluth et al., 2012). For safety or tolerability reasons, certain medications might be avoided because of comorbid conditions. More important than the mere presence of comorbidity is the concurrent use of other pharmacological substances, including prescription and over-the-counter medication, nicotine and alcohol, illicit drugs, supplements, and herbal preparations. Drug interactions mainly occur in the liver (affecting drug metabolism), in the kidneys (affecting drug clearance), or in the CNS (influencing therapeutic or adverse effects). Depending on the drugs and the type of interaction, this can result in a less than optimal therapeutic benefit, can potentiate known side effects, or can cause unexpected toxic effects. Patients should be systematically queried about their use of all types of drugs. Drug–drug interaction information should be used to avoid selecting medications that might adversely interact with anything the patient is taking.

More than 90% of elderly persons take at least one medication. A majority takes two or more drugs. Aging affects the pharmacokinetics and pharmacodynamics of drugs. The volume of distribution of most drugs is decreased in the elderly, and the distribution is shifted toward greater drug accumulation in fat stores over time. Plasma proteins decrease with age, especially in debilitated or undernourished patients, resulting in a greater proportion of protein-bound drugs existing as a free fraction. Age-related decreases in hepatic blood flow and the activity of some liver enzymes may result in decreased metabolism of many drugs. Renal function decreases with age. This is especially important with lithium, but also is relevant for drugs that are eventually renally cleared after liver metabolism. Pharmacodynamic changes associated with aging affects the sensitivity of elderly patients to pharmacological drug effects, especially adverse effects.

The net effect of these age-related changes is that psychotropic drugs typically are associated with expected, but exaggerated adverse effects in elderly compared with younger patients. Also, some drugs are associated with adverse effects that are unique to the elderly. Falls are the single most important serious complication associated with prescription and nonprescription drug use in the elderly. All psychotropic drugs increase the risk of falls. No particular drug or drug class should be considered risk-free. Falls are caused by sedation, confusion, vision changes, blood pressure effects, cardiac rhythm disturbances, balance problems, and neuromuscular incoordination. Elderly patients should be started on low doses and dose titration should be slower. The targeted therapeutic dose generally is lower for elderly patients, but some will still require higher doses within the recommended dose range.

When depressed patients do not respond adequately to an initial antidepressant monotherapy, the two main approaches are switching or combination/augmentation. For patients taking medication, psychotherapy can be considered as a viable switch option or augmentation option. Whether to switch or combine/augment medications depends on the availability of comparative data on the relative efficacy, tolerability, and acceptability of next-step treatment options. Based on placebo-controlled studies, the best established augmentation strategies are thyroid hormone, lithium, and SGA drugs. Other medication combination/augmentation approaches have not been as well studied, but they can be appropriately considered by experienced treatment specialists based on available clinical data. Unfortunately, there is virtually no direct comparative effectiveness data on the relative efficacy, tolerability, and acceptability of different combination/augmentation strategies described in this chapter. In STAR*D, an equipoise stratified randomized

design was used, such that patients could accept or decline particular treatments (similar to what happens in usual clinical practice) as long as sufficient options were left that allowed a randomization between at least two different options (Wisniewski et al., 2007). Most patients only agreed to have their medication either switched or augmented, and relatively few patients agreed to do both. As a result, definitively comparing augmentation and switching strategies could not be done.

All patients should be counseled about the potential benefits of exercise for depression, anxiety, and other psychiatric disorders, as well as for their general health and fitness. Realistic exercise recommendations should be given, appropriate for their health and compatible with their lifestyle. Because weight gain and metabolic disturbances are associated with depression and with the use of many psychotropic drugs, nutrition counseling is equally important.

Even though there is little empirical evidence to support the superior effectiveness of combining psychotherapy and pharmacotherapy for depressive disorders with comorbid anxiety disorders, substance use disorders, personality disorders, or ADD, patients who have refractory or chronic depression together with these comorbidities may derive benefit from combination therapy. Different psychotherapy models have been developed for these disparate disorders, but an active psychoeducational and skills-oriented approach to psychotherapy, which emphasizes practical interpersonal, cognitive, and behavioral interventions that are individually tailored to help achieve well-defined goals, is a common element of many effective therapies. Effectively combining therapies requires interdisciplinary coordination between psychotherapist and pharmacotherapist. Pharmacotherapy and psychotherapy can each be provided within a clearly focused and rigorous conceptual model of treatment that is delivered collaboratively.

For many depressed patients with medical comorbidity, single interventions alone (i.e., pharmacotherapy or psychotherapy) may not be as effective as collaborative care interventions, which incorporate multidisciplinary coordination among mental health specialists, primary care physicians, and nurses or other care managers (Baumeister & Hutter, 2012). Collaborative care has been shown to be effective for depressed patients with various medical conditions, although the cost-effectiveness of these interventions has not been determined.

A significant proportion of depressed patients do not have a satisfactory response to sequential trials of various drug–drug and drug–psychotherapy combinations. For these patients with chronic TRD, ECT historically has been considered the treatment of choice, but it may not be efficacious, well tolerated, or acceptable to many patients, or it may be contraindicated. Alternative approaches for patients with chronic TRD include various types of neuromodulation therapies and neurosurgical therapy procedures. Noninvasive neuromodulation therapies for patients with TRD include TMS. Among the invasive neuromodulation therapies, VNS is appropriate for ECT-intolerant or ECT-resistant depression, although patients might prefer to try TMS first. Other investigational invasive neuromodulation therapies include DBS, but this has not yet been demonstrated to be effective for chronic TRD in controlled studies. Neurosurgical lesioning procedures would then be considered as a treatment of last resort. ECT, TMS, VNS, DBS, and other similar interventions are used adjunctively with ongoing pharmacotherapy and psychotherapy, necessitating close collaboration among psychiatrists, neurosurgeons, and psychologists or other nonmedical therapists.

Conclusions

A large number of antidepressant medications and other psychotropic drugs, various depression-focused psychotherapies, and several neuromodulation therapies are available for the treatment of depression. Many drugs or psychotherapies are used for the treatment of other psychiatric disorders or medical conditions, and they should be considered relevant when these comorbidities exist with depression. Selecting (or avoiding) treatments or treatment combinations for depression must take into account the clinical implications of the presence of any comorbid disorder(s). Because comorbidity is associated with depressive chronicity and treatment resistance, various approaches to treating chronic depression or TRD have been investigated. Treating depressed patients with comorbid psychiatric, personality, or medical disorders is a clinical challenge that requires effective multidisciplinary collaboration.

Future Directions

Controlled studies have demonstrated the efficacy of specific depression treatments or treatment combinations, and many are used for treating depression with certain comorbidities, but there is a need for comparative effectiveness studies (i.e., efficacy, tolerability, safety, acceptability, and cost)

across interventions specifically targeting depressed patients with comorbid disorders. Most treatment interventions are investigated in short-term studies, but there is a need for long-term outcome studies of depression with comorbidity to determine treatment effects over time on depression outcomes, quality of life, other functional outcomes, and health-care utilization. The collaborative care model is effective for depressed patients with medical comorbidity in medical settings, but the cost-effectiveness of this model has not been established. For patients with severe chronic TRD, who have multiple comorbidities, a multidisciplinary collaborative care model should be developed and investigated.

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CHAPTER

32

The Role of Community- and Home-Based Interventions in Late-Life Depression

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Abstract

Depressive disorders are highly prevalent and among the most debilitating conditions in late life. If untreated, depression has profound effects on quality of life and health; it also increases the risk for dementia, other comorbidities, functional decline, and mortality. Although primary care is the principal setting for the detection and treatment of depression, older adults and particularly, minorities do not always receive evidence-based treatment guidelines. Thus, new care models are urgently needed. This chapter considers the role of community- and home-based approaches to depression care, their theoretical underpinnings and advantages, and exemplary programs. Twenty-three rigorously tested community- and home-based interventions with positive depression outcomes are identified, suggesting a robust and growing evidence base. Community- and home-based approaches may overcome persistent mental health disparities by reaching underserved populations, minimizing stigma by normalizing depression detection and delivering treatments at home, and increasing access to nonpharmacological approaches—such as psychosocial and behavioral approaches—for older adults who are at risk for or have late-life depression.

Key Words: depression, late-life depression, home-based approaches, community-based approaches, psychosocial approaches, behavioral approaches, mental health disparities, underserved populations

"I never realized I was depressed and learned a great deal about depression. I have a new outlook on life and think more positively about things."

—Mr. L., age 80

"They not only helped me to recognize that I had symptoms of depression and that having those feelings was a problem, but how to get myself out of it."

—Mrs. J., age 61

"I used to sit around and be depressed about [my health] and other things going on in my life. . . . I guess I'm just happy that I'm not down in the dumps anymore . . . I can get up and do things now."

—Mrs. C., age 75

[Testimonies from participants in the Beat the Blues Trial, a community- and home-based intervention model, demonstrating the potential role and efficacy of community models of depression care.

From Gitlin et al., and Get Busy Get Better, Helping Older Adults Beat the Blues (formerly Beat the Blues) team, 2012.

Introduction

Depression is one of the most debilitating conditions in late life; if untreated, it has profound effects on an older adult's everyday functioning, quality of life, and health and well-being. Depression places older adults at increased risk for significant health declines and negative consequences including dementia, prolonged inflammatory responses

following infection (Glaser, Robles, Sheridan, Malarkey, & Kiecolt-Glaser, 2003), heightened anxiety, functional decline (Lenze, Rogers, Martire, Mulsant, Rollman, et. al., 2001), exacerbation of comorbidities, and increased mortality risk (Cuijpers, Beekman, & Reynolds, 2012). Even mild depressive symptoms are associated with difficulties in performing daily activities, poor health outcomes, increased health-care utilization, and the development of major depression (Arean, 2006; Glaser et al., 2003). Depressive disorders are one of the greatest sources of disease burden and disability and an economic drain worldwide and in the United States owing in part to several critical societal trends (Bromet, Andrade, Hwang, Sampson, Alonso, et al., 2011; National Institute of Mental Health, 2010; World Federation for Mental Health, 2012). These include the unprecedented worldwide age transition; the rise of chronic illness and other risk factors for depression; and the persistence of disparities in access to diagnosis and evidence-based depression treatments (Institute of Medicine [IOM], 2012). In the United States, minorities represent the fastest-growing segment of the aging population, and this group in turn confronts multiple jeopardies including poor health, low income, and unsafe neighborhoods, all risk factors for depression. The decrease in the older white population (projected to be from 80% to 71%) will be accompanied by a significant increase in older African American (115% increase) and Latino populations (200% increase) such that by 2030, these groups will comprise 10% and 12% of the older population respectively (IOM, 2012). These trends affect the way in which mental health services need to be delivered now and into the future.

In the United States, primary care is the principal setting for the diagnosis and treatment of depression. Yet depression screening rarely occurs; in 2007, only 2.2% of primary care physician office visits involved a screen for depression of adults 19 years and older (http://www.healthypeople.gov/2020/default.aspx). Among older adults, depressive symptoms are typically underrecognized and undertreated and most older adults do not receive recommended and evidence-based depression treatments in that setting (Arean, Ayalon, Jin, McCulloch, Linkins, et al., 2008; Ell, 2006; Miranda & Cooper, 2004). A study of primary care patients showed that of 2,321 study participants, 304 (13.1%) screened positive for a depressive disorder; however, of those, only 31.0%, or one third, were subsequently diagnosed by their physician (Ani, Bazargan, Hindman, Bell, Farooq, et al., 2008). The gap in detection and treatment is even more pronounced among adults who are of low income, from diverse racial and ethnic groups, and the oldest old (Wang, Lane, Olfson, Pincus, Wells, & Kessler, 2005). Compared with their white counterparts, older African Americans are at greater risk for not receiving standard depression care such as having symptoms identified and being given treatment options or participating in psychotherapy and other evidence-based treatments (Arean, Ayalon, Hunkeler, Lin, Tang, et al., 2005; Cooper, Gonzales, Gallo, Rost, Meredith, et al., 2003; Cooper-Patrick, Gallo, Powe, Steinwachs, Eaton, & Ford, 1999). However, when treatments are offered, it has been shown that this group greatly benefits (Arean et al., 2005; Arean, Gum, Tang, & Unutzer, 2007; Cooper et al., 2003; Cooper-Patrick et al., 1999; Joo, Morales, de Vries, & Gallo, 2010). Whereas an average of a mere two minutes is spent in physician-patient encounters on mental health concerns with older adults, even less time is afforded to older African Americans (Tai-Seale, McGuire, Colenda, Rosen & Cook, 2007).

Given the crisis in mental health care, there is an urgent need for novel care models that involve new partners, health providers, and care sites and that complement/extend primary care or serve as alternatives to it; only then can we make sure that depression care is accessible and culturally appropriate to an increasingly diverse older adult population (Alexopoulous & Bruce, 2009; Callahan & Hendrie, 2010; IOM, 2012).

This chapter explores the role of community- and home-based models for detecting and treating depression in older adults and reducing mental health disparities for minority populations. Examined first is the prevalence of depression among older adults, followed by a consideration of the role of community- and home-based approaches, the theoretical underpinnings of these approaches, and their advantages. Then, exemplary programs are discussed with particular attention to interventions for at-risk populations such as minorities. Finally, issues related to the translation and implementation of programs into real-world contexts and directions for future research are explored.

Prevalence of Depression

Depression is among the most prevalent mental disorders among older adults worldwide and in the United States. It is estimated that 121 million people worldwide have depressive disorders, with a significant upward trend expected over the

next 20 years (Bromet et al., 2011). The burden of depression in the United States is considered to be equally high. Of 35 million older adults, an estimated 7 million suffer from depression—2 million with a depressive illness and 5 million with subsyndromal or minor depression (National Institute of Mental Health, 2010; Shellman & Mokel, 2010).

Despite much research on the prevalence of depression, there is considerable variation across studies. Whereas major depression appears to be relatively rare (less than 2% reported by most studies), minor depression and depressive syndromes of clinical significance are more common, with most studies reporting an average prevalence rate of 15% to 17% (Blazer, 2002).

Rates differ depending upon the setting studied and clinical population. For example, it has been estimated that rates in primary care tend to range from 5% to 10%. However, a study involving one of the largest and most diverse cohorts of depressed older adults in that setting (N = 1,801), found that 46% of subjects reported receiving depression treatment in the three months prior, a rate much higher than previously reported (Unutzer, Katon, Callahan, Williams, Hunkeler, et al., 2003).

The prevalence of depression is much higher for older adults with physical health problems and functional disabilities, with some studies reporting rates up to 25% to 33%. Major depression may be twice as common among older adults receiving home care than those receiving primary care, with very few being treated for their depression (Bruce, McAvay, Raue, Brown, Meyers, et al., 2002). Depression may also be high for certain subgroups among the elderly. For example, close to 50% of caregivers of persons with dementia report depressive symptoms (Schulz, O'Brien, Bookwala, & Fleissner, 1995).

The prevalence of depression may be higher than previously reported among older minorities. For example, among African Americans, early reports indicated rates ranging from 7% (Eaton & Kessler, 1981) to 18.3% (Stallones, Marx, & Garrity, 1990), with a median of about 17%; more recent research suggests a much higher prevalence rate. The African American Health Study of 998 community-dwelling African Americans found that 21.1% of African American women, those living in inner cities, and individuals with functional difficulties had clinically relevant levels of depressive symptoms (Miller, Malmstrom, Joshi, Andresen, Morley, & Wolinksky, 2004). Of 150 older poor African Americans attending outpatient rehabilitation, 30% scored positively for depression (Kurlowicz, Outlaw, Ratcliffe, & Evans, 2005). In a survey of 153 older African American members of a senior center, 24.2% reported mild to moderate depressive symptoms (Gitlin, Chernett, Dennis, & Hauck, 2012). In a depression trial (Get Busy Get Better, Helping Older Adults Beat the Blues) involving medically compromised older African Americans receiving temporary home support services, of 440 screened for depressive symptoms, 31% (137) scored with mild to moderate depressive symptoms (Gitlin, Harris, McCoy, Chernett, Jutkowitz, & Pizzi, 2012). Depression rates are also high among individuals with low income and poor health (George & Lynch, 2003; National Mental Health Association, 2004). Homebound older adults, of whom there are approximately 3.6 million in the United States, suffer from metabolic, cardiovascular, cerebrovascular, and musculoskeletal disease as well as cognitive impairment and dementia, all risk factors for depression, and they have higher depression rates than the general elderly population (Qiu, Dean, Liu, George, Gann, et al., 2010). Prevalence rates for other older minority groups are underreported but are suspected to be high.

Although depression tends to be more prevalent among women than men, it is unclear whether this holds true across racial/ethnic groups. A study with over 1,400 diverse older adult Medicare recipients of the North Manhattan Aging Project (NMAP) found that gender differences in depressive symptoms varied by race and ethnic group. For example, Latinas were three times as likely as black women to express affective suffering (Yancu, 2011). Likewise, in the senior center survey of 153 members mentioned above, the prevalence and severity of depressive symptoms were similar for African American men and women (Gitlin et al., 2012).

Although rates vary considerably, it is clear that many older adults from diverse racial and ethnic groups and with different health states and living conditions are at risk for or experience depressive disorders.

Potential Roles of and Evidence for Community- and Home-Based Approaches

Community, in the context of this chapter, refers to a vast array of settings and services such as senior housing, senior centers, adult day services or health and human service programs offered through area agencies on aging or the aging network. The aging network alone, a federally and state-funded system in the United States, provides a wide range of community-level social services to over 9 million older adults, many of whom are vulnerable and

underserved (Gitlin & Harris, 2009). Despite their outreach to and involvement with millions of older adults, these services and settings for the most part do not engage in systematic depression care (detection and treatment), yet their potential impact on mental health could be considerable.

Figure 32.1 displays the potential roles of community- and home-based approaches across a hypothetical model of disease progression, from no to severe symptomatology. Whereas traditional depression management approaches in primary care or mental health settings focus on treatment and drug therapies, communities can have a broader function and offer a wider range of novel approaches and nonpharmacological therapies.

As shown, the roles of community- and home-based approaches vary based on level of depressive symptoms. Roles may involve prevention, education, and risk reduction for older adults without symptomatology; education, risk reduction, and early detection for older adults with subclinical and mild symptoms; and education, treatment/symptom management, and referral and linkage for older adults with moderate to severe depressive symptoms. Several roles and associated activities are similar across the levels of depression severity and may include ongoing depression screening and detection, depression education (e.g., symptom recognition), and reduction of risk factors (e.g., social isolation, medication concerns, lifestyle and chronic disease management issues including adherence to diet, exercise, medications). Other roles and associated activities are specific to the level of symptom severity.

With increasing symptom severity, the role of communities may expand from detection and education to delivery of nonpharmacological treatments at home or on site in the community (e.g., senior center, adult day care). These treatments may include but are not limited to care management, problem solving, behavioral activation, counseling, and, importantly, referral and linkage to other mental health services for individuals with significant mental health issues or depression medication management. Also, an important role for those with the most severe symptoms may be monitoring symptoms, providing ongoing education and strategies for managing symptoms, supporting medication adherence, and linking this group to needed specialist care.

A growing body of evidence supports the roles suggested in Figure 32.1. As to depression detection, the U.S. Preventive Services Task Force (2009) indicates that there is adequate evidence for the use of a variety of screening instruments including asking two simple questions about mood and anhedonia ("Over the past two weeks, have you felt down, depressed, or hopeless?" and "have you felt little interest or pleasure in doing things?"). However, the task force also recommends that positive screening

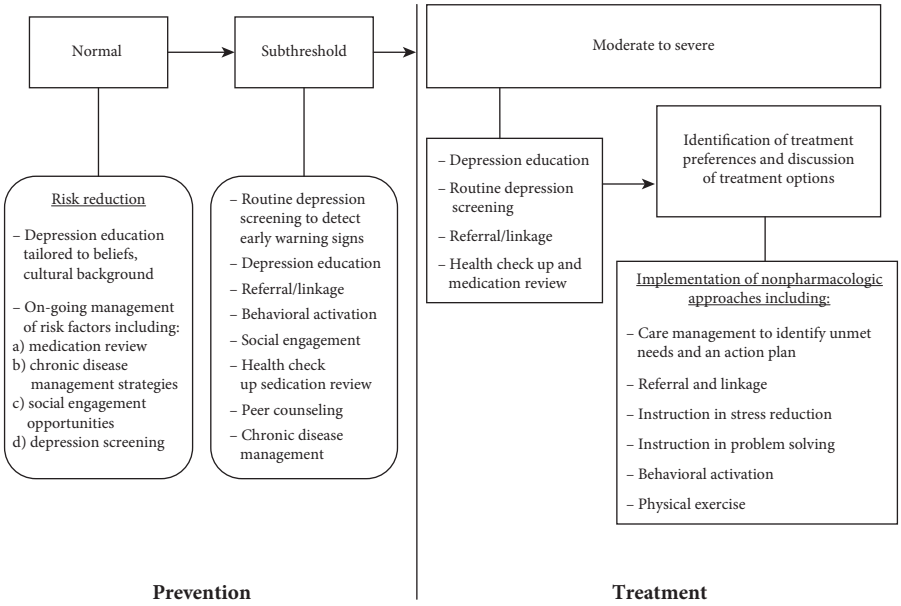

Figure 32.1 Opportunities for community- and home-based approaches along a hypothetical trajectory.

tests be followed by a full diagnostic interview using standard diagnostic criteria; this may be difficult for communities without access to clinical experts. Also, the task force suggests that screening alone appears to be insufficient and should be conducted only when staff-assisted depression care supports are in place to assure accurate diagnosis, effective treatment, and follow-up. While the task force reviewed evidence generated by research on primary care, its recommendations would appear relevant to community settings. Thus to engage in depression management, community-based agencies would need to retool to make sure that they have an appropriate infrastructure, including staff knowledgeable in depression, linkages to mental health experts, and an ability to facilitate the provision of evidence-driven treatment and follow-up support.

Strong evidence for a treatment role also exists. While community- and home-based care models for mental health services are not new, recent efforts have yielded well-defined and tested models (Bruce, 2010). An expert panel review of 116 community-based studies conducted between 1997 and 2005 reported that the strongest evidence existed for depression care management interventions delivered at home. However, the evidence base for education and skills training interventions was mixed, particularly for caregivers. There was little evidence to support the use of geriatric health evaluation and management or physical rehabilitation and occupational therapy interventions to address depression (Frederick, Steinman, Prohaska, Satariano, Bruce, et al., 2007). The panel concluded that multicomponent approaches may be most effective. While some interventions that are not directed at depression, such as rehabilitative interventions, may have some positive mood effects, treatments specifically for depression are preferred.

Another recent systematic review of seven depression treatment studies with older adults from diverse racial and ethnic groups published between 1990 and 2010 found positive depression outcomes for five studies. Collaborative care models showed the most promise for African American and Latino older adults (Fuentes & Aranda, 2012). Treatment settings included primary care, social service agencies, inpatient facilities, subsidized housing, and home care.

The few studies evaluating intervention delivery suggest a preference by older adults for home- versus clinic-based treatment (Kelley-Moore & Ferraro, 2004). Some research suggests that home-based sessions may lead to better treatment acceptance (Hinton, Zweifach, Oisbi, Tang, & Unutzer, 2006), fewer nursing home admissions as well as inpatient care days; they may also be more cost-effective (Utsey, Adams, & Bolden, 2000).

Theoretical Frameworks Underlying Community and Home-Based Approaches

Because the etiology of depression remains unclear, competing theoretical frameworks have guided research in this area. Community- and home-based approaches typically assume a behavioral explanation, linking mood to daily life stressors; they address functional triggers and consequences of depressive moods. Thus depression is viewed as a consequence of environmental contingencies that decrease healthy responses within one's behavioral repertoire and increase avoidance of aversive stimuli. In this framework, depression serves as a coping strategy to avoid environmental circumstances that involve low levels of positive reinforcement and minimal control. Behaviorally oriented depression treatments seek to restore balance by realigning the person and his or her environment.

Using a behavioral framework, most community- and home-based depression interventions are concerned with reducing risk factors, promoting social connectedness, helping people engage in meaningful activities, establishing doable daily routines, and managing chronic illnesses—that is, complying with lifestyle adjustments and complex medication regimens. Treatments typically focus on educating individuals about depressive symptoms and their management and activating individuals through problem-solving therapy or behavioral activation techniques.

A growing evidence base supports a behavioral treatment approach. Component analysis studies of cognitive behavioral therapy have identified behavioral activation as the active ingredient, with follow-up studies showing it to be an effective stand-alone approach (Lejuez, Hopko, & Hopko, 2001; Hopko, Lejuez, Ruggiero, & Eifert, 2003). The focus of activation therapy is on helping individuals identify and complete behavioral goals despite the presence of negative mood states. The goal is to break the behavior-mood cycle by moving a person from avoidance to action. Although the focus is on activation, cognitive and emotional processes are believed to change as a consequence of engaging in positive events and experiencing positive contingencies (Hopko et al., 2003).

Adaptive behavioral models such as Lawton's competence-environmental press may also be

applicable (Lawton & Nahemow, 1973). This adaptive model suggests that a person's behavior is a function of the interaction of his or her competence level and environmental demands. For depressed older adults, the balance between the demands of their environment and their abilities to respond may be disrupted resulting in maladaptive behaviors and poor affect (Kiosses, Arean, Teri, & Alexopoulos, 2010). Interventions directed at helping individuals become rebalanced by reducing environmental demands and increasing use of positive coping strategies may be effective.

Examples of Community- and Home-Based Care Models

Table 32.1 summarizes 23 studies of community- and home-based depression interventions for older adults conducted from 2000 to the present. A wide range of novel interventions are listed with all but two tested using a randomized trial design. All studies reported immediate treatment benefits including reductions in depressive symptoms and improvements in quality-of-life domains such as functional disability, anxiety, emotional well-being, depression knowledge, and pain. Some studies report long-term maintenance of improvements as far out as 12 months from treatment (Gitlin et al., 2012; Lamers, Jonkers, Bosma, Kempen, Meijer, et al., 2010).

Commonalities across tested interventions include their multicomponent nature, inclusion of care management as a central feature, delivery of the intervention in the home or a local community setting, strategies that are tailored to people's needs, and a focus on the "here and now" or solving present living circumstances as opposed to using introspective psychotherapeutic approaches. For example, the "PATH" intervention program (Kiosses et al., 2010) helps patients reduce depressive symptoms through the use of problem-solving therapy, implementation of environmental adaptations and inviting family caregiver participation (Kiosses et al., 2010). The Pearls program used problem-solving to address current life challenges (Ciechanowski, Wagner, Schmaling, Schwartz, Williams, et al., 2004). Healthy IDEAS (Casado, Quijano, Stanley, Cully, Steinberg, et al., 2008; Quijano, Stanley, Peterson, Casado, Steinberg, et al., 2007) and the Get Busy Get Better, Helping Older Adults Beat the Blues Program (formerly Beat the Blues) (Gitlin, Harris, McCoy, Chernett, Jutkowitz, & Pizzi, 2012) each used behavioral activation as the core treatment modality.

Two programs in particular illustrate the important role of community agencies and home treatment approaches—Healthy IDEAS and Get Busy Get Better, Helping Older Adults Beat the Blues. Building upon previously tested approaches and offered through the aging network, Healthy IDEAS (Identifying Depression, Empowering Activities for Seniors), involves systematic screening, care management, depression education, referral and linkage, and engaging clients in behavioral activation by case managers in service agencies. The approach showed important but modest positive client outcomes including enhanced depression knowledge, decline in symptomatology, and clinician adoption (Casado et al., 2008). However, Healthy IDEAS was not tested in a randomized trial, and less than half (44.7%) of the 94 participants received behavioral activation, with only a small percentage of participants being African American.

Get Busy Get Better (Helping older adults beat the blues; GBGB) has built upon the successes and lessons learned from prior depression treatment efforts, specifically the Healthy IDEAS and Pearls approaches, and targeted older African Americans. It was designed for delivery by community-based organizations such as senior centers. It differs from previous efforts in several important ways. First, its delivery is integrated within the staffing patterns and daily routines of a senior center versus a mental health clinic or primary care setting, thus enhancing the potential for normalization and sustainability in that setting. Second, it is culturally relevant to the target population, its name reflects the characterization of depression by the target group, and treatment components resonate with preferred coping approaches of older African Americans. For example, as activity is a key coping mechanism for older African Americans, behavioral activation is an essential component of GBGB, helping participants to reengage in self-identified meaningful activities (Agarwal, Hamilton, Crandell, & Moore, 2010). Although each treatment component of GBGB was tested previously in other trials, their combination has not been systematically evaluated or tested with older community-dwelling African Americans. The GBGB trial involved 208 participants with mild to severe depressive symptoms who were screened at a local senior center by care managers. Participants were randomly assigned to a wait list control or a treatment group, which received care management, referral/linkage, stress reduction techniques, depression education, and behavioral activation in 10 one-hour sessions over four months. The control group received GBGB after the initial four months. At the end of this period, GBGB participants

Table 32.1 Examples of Community- and Home–Based Depression Programs

Program	Target Population	Intervention	Design	Outcomes
Problem-Solving Therapy Areán et al., 2010	Older patients with depression and executive dysfunction	Twelve weekly sessions. The problem-solving model is taught during the first five weeks. The seven remaining sessions are for refinement of problem-solving skills. Participants set goals, create action plans, and evaluate the effectiveness.	RCT *N* = 221 Control received supportive therapy	↓Depression Similar outcomes during first six weeks between groups. At weeks 9 and 12 the problem-solving group had greater reduction in depressive symptom severity and a greater remission rate.
Healthy Ideas (Identifying Depression, Empowering Activities for Seniors) Casado et al., 2008; Quijano, 2007	Community agencies providing care management to older adults	Screening and assessment by care managers Depression education and where to get help. Referral and linkage Behavioral activation	Service evaluation *N* = 94 No control group	↓Depression Enhanced depression knowledge Enhanced feeling of well-being Reduced pain
Effects of Music on Depression and Sleep Chan, et al., 2010	Older adults in Hong Kong, China, attending a community center	Four weeks, 30 minutes music per week. There were several selections of music that participants could choose from—meditative, Chinese classical, western classical, and western modern jazz.	RCT *N* = 42	↓Depression ↑Sleep quality
Effects of Music on Depression Chan et al., 2012	Older adults living at home in Singapore	Eight weeks, 30 minutes of music per week. There were several selections of music that participants could choose from—Chinese, Malay, Indian, and western slow rhythmic music.	RCT *N* = 50	↓Depression
Silver Yoga Exercises Chen et al., 2009	Older adults in eight senior activity centers in Taiwan	Six months of silver yoga exercises, 70 minutes per session, three sessions per week.	RCT *N* = 128 Site randomized Wait list control	↓Depression ↓Daytime dysfunction ↑Sleep quality ↑Physical and mental health perception
Collaborative Care Model for Management of Depression in Older People Chew-Graham et al., 2007	Patients 60 years and older referred by 43 practices in a Primary Care Trust in North West England GDS > 5 MMSE > 24	Twelve weeks, six face-to-face visits and five via telephone. Community psychiatric nurse in primary care was the care coordinator. Intervention included education, advice about medication, facilitated self-help intervention (SHADE), and sign posting for other services.	RCT *N* = 105	↓depression

(continued)

Table 32.1 Continued

Program	Target Population	Intervention	Design	Outcomes
Effect of Tai Chi Chou et al., 2004	Community-dwelling older adults who attend a psychogeriatric outpatient clinic in Hong Kong	Three months, three 45-minute sessions per week.	RCT *N* = 14	↓Depression
Program to Encourage Active, Rewarding Lives for Seniors (PEARLS) Ciechanowski et al., 2004	Home-based program for older adults with minor depression or dysthymia in metropolitan Seattle	Eight 50-minute in-home sessions over 19 weeks involving: Problem solving therapy Social and physical activation Education, monitoring for antidepressant use Work with physician and psychiatrist to recommend medications	RCT *N* = 138	↓Depression ↑Quality -of life and functional well-being ↑Emotional well-being
Problem-Solving Therapy in Home Care (PSTHC) Gellis et al., 2010	Homebound older adults with cardiovascular disease receiving acute home-care services	Six one-hour sessions and weekly telephone calls over six weeks involving: Depression education Problem-solving skills Pleasurable activity scheduling Homework	RCT *N* = 38 Control group plus education	↓Depression ↑Satisfaction with care No change in anxiety
Gellis et al., 2007	Home-care older adults with a CES-D ≥ 22 and MMSE ≥ 24.	Six one-hour sessions to define the problem, generate alternative solutions, evaluate consequences, select one to implement, monitor, and evaluate.	RCT *N* = 40 All patients received antidepressants	↓Depression ↑Quality of life ↑Problem solving ability
Get Busy Get Better, Helping Older Adults Beat the Blues (BTB) Gitlin et al., 2012	Community-dwelling African Americans 55 years and older	Ten one-hour sessions at home over four months by licensed social workers involving: Depression education Care management Referral and linkage Behavioral activation Stress reduction techniques	RCT *N* = 207 Wait list control	↓Depression ↓Anxiety ↓Functional disability ↑Quality of life

Coping with Depression (CWD) Haringsma et al., 2006	Community-dwelling older adults with subclinical depression and major depressive disorder in the Netherlands	Ten weekly two-hour sessions in groups of 6 to 13 participants (not all were in the study). Social leaving view of depression. Skills taught: relaxation, increasing pleasant activities, constructive thinking, improving social skills, and maintaining treatment gains.	RCT *N* = 119 Wait-list control	↓Depression ↓Anxiety
Geriatric Psychiatry Outreach (GO) Program Johnston et al., 2010	Older adults with difficulty getting to an office-based setting. Primary diagnoses were depression and dementia	In-home psychiatric evaluation and treatment with an average of 4.2 in-home visits with additional contact made by phone, email, and fax for follow-up and referrals.	Service evaluation *N* = first 100 patients No control group	Common reason for discharge was referral back to primary care physician
Depression in Late Life Intervention Trial of Exercise (DeLLITE) Kerse et al., 2010	Older adults age 75 years plus in Auckland, New Zealand	Eight one-hour visits in-home with a nurse who designed an individualized physical activity program over six months. Participants were asked to identify a functional goal and were encouraged to get a companion to assist them with the exercises. They were to do the exercises and walk for 30 minutes three days a week.	RCT *N* = 193 Attention control received social visits	↓Depression ↑Quality of life Results were similar in both groups. There was no significant difference between intervention and attention control.
Problem Adaptation Therapy (PATH) Kiosses et al., 2010	Older adults with major depression, cognitive impairment, and disability using a home-delivered meals program	Twelve-week intervention delivered in home focusing on the ecosystem of the patient and his or her home environment. Components include: Problem solving therapy Environmental adaptation Pleasurable activities Caregiver participation	RCT *N* = 30 Control group was given home-delivered supportive therapy	↓Depression ↓Disability
Life Review Therapy Korte et al., 2012	Adults age 55 years plus with moderate depressive symptoms (≥ 10 on CES-D) from Dutch mental health services	Eight two-hour sessions with four to six participants in each group. "The stories we live by" revolves around three core elements, (1) integration of difficult life events from the past, (2) development of life stories to cope with present life events and formulate goals, and (3) retrieval of specific positive memories.	RCT *N* = 202	↓Depression ↓Anxiety Effects were maintained at three- and nine-month follow-ups

(continued)

Table 32.1 Continued

Program	Target Population	Intervention	Design	Outcomes
Depression in Elderly with Long-Term Afflictions (DELTA) Lamers et al., 2010	Adults age 60 years and older with minor depression or mild to moderate major depression and either type 2 diabetes or COPD. Recruited from primary care in the Netherlands.	Minimal Psychological Intervention (MPI) delivered in home by trained nurses. Number of visits from 2 to 10 with average of four one-hour sessions. The intervention consists of five phases: (1) exploration of patient's feelings, cognition and behavior; (2) patient keeps a diary of symptoms, thoughts, and behaviour: (3) patient is challenged to link mood to behaviour; (4) self-management approach is introduced; and (5) evaluation of progress is made.	RCT *N* = 361	↓Depression Effects were maintained at three- and nine-month follow-ups
Tai Chi Chih Lavretsky et al., 2011	Adults age 60 years plus with unipolar major depressive disorder (HDRS ≥ 16). MMSE ≥ 26	All participants were treated with Lexapro for four weeks. At the four-week mark they were randomized to either Tai Chi Chih or Health Education. Ten weeks of two hours per week.	RCT *N* = 112(only 73 were randomized at the four-week mark) Attention control received health education	↓Depression ↑ SF-36 physical functioning and cognitive scores
Life Story Workshop Mastel-Smith et al., 2007	Adults age 60 years and older living independently in the community.	Ten weeks, once-a-week two-hour workshop during which the group wrote stories about their lives to share with the group. The group was also encouraged to write between meetings.	RCT *N* = 33	↓Depression
Looking for Meaning Pot et al., 2010	Adults age 50 years plus and a score of 5 or greater on the CES-D	Groups of eight participants met for 1 sessions of two hours each. Each session was centered on a topic related to the life course.	RCT *N* = 171 Control group watched a 20-minute video: "The Art of Growing Older"	↓Depression Females and those with baseline depressive symptoms of ≥ 16 on the Ces-D showed a greater reduction in depressive symptoms. Effect still present at six-month follow-up.

Psychogeriatric Assessment and Treatment in City Housing (PATCH) Program Rabins et al, 2000	Older adults with serious psychiatric disorders living in six urban public housing sites	Psychiatric nurse–based mobile outreach program involving: Educating building staff to be case finders Assessments in residents' apartments In-home psychiatric care Addressing medical and social comorbidities through care management	RCT *N* = 945 stage 1 screening *N* = 237 stage 2 case finding	↓Psychiatric symptoms ↓Depression
Life Review Therapy Serrano et al., 2004	Adults age 65 years plus with clinically significant depressive symptomatology (≥ 16 on the CES-D) and no dementia (≥ 28 on MMSE) in Almansa, Spain.	Life-review therapy was completed over four weeks. Each week the focus was on a different life period (childhood, adolescence, adulthood, and summary). There were 14 prepared questions for each session to prompt memories.	RCT *N* = 43 Control group received visits for social assistance	↓Depression ↑Life satisfaction
Group Reminiscence Therapy Zhou et al., 2012	Community-dwelling adults age 60 years plus living with mild to moderate depression (GDS = 11 to 25).	Six weeks of group reminiscence therapy and health education.	RCT *N* = 125 Control group received health education over three sessions	↓Depression ↑Affect balance No change in self-esteem

compared with controls had reduced symptomatology; improved knowledge about depression and symptom recognition; improved well-being, quality of life, and behavioral activation; and less anxiety; and fewer functional difficulties. Also, more GBGB participants were in remission than control group participants (43.8% vs. 26.9%). At eight months, control-group participants demonstrated similar benefits following treatment, although the initial GBGB group maintained the most benefits (Gitlin et al., 2012). Both Healthy IDEAS and GBGB illustrate that a community- and home-based approach is successful at detecting depression, enhancing access to treatment, and improving mood.

Interventions specific to caregivers of persons with dementia have shown inconsistent results with regard to reducing depressive symptoms, with some showing benefit (Belle et al., 2006; Mittelman, Ferris, Shulman, Steinberg, Ambinder, et al., 1995) and others not (Gitlin et al., 2003) although other important mood and well-being outcomes were found. Most caregiver interventions are not designed to address depressive symptoms. However, some may have a positive impact on mood by alleviating contributing factors to depression.

Despite a growing, strong evidence base for community approaches, more research is warranted to improve outcomes, tailor strategies effectively and systematically, and determine cost, cost-effectiveness, and long-term results. A promising direction for future intervention research is the testing of technologies to enable better outreach and reduce costs associated with travel to homes, particularly in rural areas. Preliminary evidence from recent trials suggests that telephone-delivered treatments are promising (Rollman et al., 2009; Schulberg, Belnap, Houck, Maxumdar, Reynolds, et al., 2011).

Advantages of Community- and Home-Based Approaches

Key advantages of community and home-based approaches include normalizing depression detection activities, overcoming stigma associated with depression and its treatment in traditional settings, providing access to nonpharmacological approaches as first-treatment lines, and linking older adults with serious mental illness to the medical and specialized mental health care they may need (Table 32.2). Community- and home-based approaches may afford important advantages for specific subgroups of older adults. Evidence suggests that primary care providers overprescribe medication for individuals with subthreshold symptomatology, with few resulting benefits. These individuals may be better treated in naturally occurring community settings using nonpharmacological approaches as first-line treatments. Because low-income older adults may have poor access to resources such as transportation as well as poor physical mobility and unmet care management needs, interventions that address contextual factors contributing to mood disorders are needed (Arean et al., 2010).

Table 32.2 Key Advantages of Home- and Community-Based Models

- Overcome barriers to traditional care including transportation, mobility, stigma
- Provide opportunities for tailoring to care preferences not necessarily afforded in primary care
- Preference for nonpharmacological approaches more easily accommodated than in primary care
- Enable closer examination and management of the living context and its impact on mood and activity
- Facilitate identification and modification of the functional consequences of depressive moods (e.g., reduction in activity and social connectedness)
- May be less of a tendency to overprescribe medications and to try nonpharmacologic approaches as first-line of treatment

Providing depression treatment at home is also advantageous for home-bound older adults. This group may need more aggressive management of depressive symptoms because accessing services may be challenging and the home environment may impose functional difficulties that would go unrecognized in a clinic setting (Ayalon, Fialová, Areán, & Onder, 2010). Similarly, community and home-based approaches are advantageous for individuals who prefer to try a nonpharmacological approach initially. A survey of 1,602 depressed older primary care patients in a multisite clinical trial found that most preferred counseling over medication. However, counseling is infrequently available in usual primary care (Gum, Arean, Hunkeler, Tang, Katon, et al., 2006). Nonpharmacological approaches are also a strong preference among minority populations (Mills, Alea, & Cheong, 2004).

Finally, community and home-based approaches may address the mental health disparity gap for older minority populations. This gap may be due in part to clinical misinterpretation of symptoms and cultural mistrust (Mills et al., 2004; Whaley, 2001). Cultural mistrust, an important psychological phenomenon, may lead clinicians to misinterpret its expressions as mental illness (e.g., paranoia). Alternatively, cultural mistrust may contribute to the reluctance of older minorities

to report feelings of distress in primary care settings. Because depression is stigmatizing and often considered a social embarrassment or sign of personal weakness, this also may contribute to the underutilization of formal mental health services (Alvidrez, 1999; Cooper et al., 2003; Crystal, Sambamoorthi, Walkup, & Akincigil, 2003; Diala, Muntaner, Walrath, Nickerson, LaVeist, & Leaf 2000; Primm, Cabot, Pettis, Vu, & Cooper, 2002; Unützer, et al., 2003). Embedding and routinizing depression screening in community agencies may help to overcome cultural mistrust.

Limitations of Community- and Home-Based Approaches

One limitation of community- and home-based approaches is the lack of integration with traditional mental health care services and primary care to effectively address interrelated physical health and/or other serious mental health needs of older adults. Whereas older adults may initially benefit from depression care management at the community level, they may need additional supports to address health factors contributing to their poor mood, such as managing their chronic illness, medications, or functional disabilities in addition to benefiting from other skilled mental health interventions, including in-depth psychotherapy. Collaborative care models in primary care result in significant improvements in depression outcomes for all racial and ethnic groups (Arean et al., 2005). Extending the collaborative model to include a seamless interface with key community agencies, such as senior centers or, alternatively, extending community-based treatments to link collaboratively with other health care professionals and primary care is a promising approach warranting investigation.

Another limitation is workforce preparation. Staff members of community-based agencies typically require training in depression detection and care approaches. Community-based agencies may not have the appropriate personnel or resources to hire qualified staff to implement skilled depression care treatments. Lack of access to geropsychiatrists or other skilled mental health professionals for consultation and referral is a related challenge. Last, it is unclear whether addressing contextual needs alone can improve moderate to severe depression or whether other treatment combinations are needed.

Translation and Implementation of Proven Community- and Home-Based Interventions

An urgent need is for the translation and implementation of proven community and home-based approaches. Integrating depression screenings and nonpharmacological treatment delivery in community settings has been difficult to achieve for several reasons. Funding for depression care is limited. Community organizations must be creative in identifying and combining and diversifying funding sources (government and foundation grants, reorganization of business model and activities to support depression care, partnering with academic organizations) to support implementation of interventions listed on Table 32.1.The delivery of and payment system for mental health services must be reorganized to support the promise of community- and home-based treatments. Although depression detection activities may be more easily absorbed into the daily operations of agencies involved in intake or care management activities in general, training in depression care and the use of standardized screening and assessment tools is still needed. Most intervention approaches require personnel with some mental health training, and agencies or community organizations may not have the funds to support their hiring and oversight.

A related challenge is the limited knowledge of the actual costs and cost-effectiveness of community- and home-based models. PEARLS has been cited to cost about $630 for its delivery, but more recent estimates based on its real-world implementation suggest that its costs are twice as high (see http://www.pearlsprogram.org/). For GBGB, the average screening cost was only $2.63 per participant and total home intervention cost (screening plus home intervention) was $584.64 over four months, or $146.16 per participant per month (Gitlin et al., 2012). Although these costs compare favorably with pharmacological treatments, they still represent a cost challenge for agencies that may not have the personnel on staff who qualify for Medicare reimbursement (Gitlin et al., 2012).

Conclusions

Depressive disorders, regardless of symptom severity, pose a serious health risk to older adults and are associated with a pernicious downward spiral. Prevention and treatment of symptoms must be taken seriously and new models of care should be implemented to overcome the limitations of traditional mental health care.

In an editorial entitled "Who Should Own Public Mental Health," Terry Brugha asked why depression care remains confined to general practitioners when so few older adults receive recommended treatments in primary care (Brugha, 2007). This chapter

responds to this query by suggesting that alternative approaches should involve community- and home-based approaches. Traditional mental health services tend to view depression as a set of isolated symptoms detached from the context of daily life. Potential sources of symptoms common among older adults—such as illness intrusion, financial and neighborhood constraints, or comorbidities—may not be considered. In contrast, community- and home-based approaches assume a more integrative stance and seek to attend to the context of daily life impinging on mood. Community-based organizations are typically trusted by the older adults in the geographic regions they serve. Thus their provision of depression care may afford numerous advantages, including overcoming societal stigma associated with traditional mental health clinic services and reaching vulnerable populations excluded from traditional treatment options. A community-based approach also offers multiple points of access to depression services (detection and treatment) for older adults versus relying on only one setting, such as primary care.

Although more research is necessary, rigorously tested community- and home-based interventions (Table 32.1) with positive outcomes exist and provide a robust and emergent evidence base to support moving forward with their implementation (Table 32.2). There is an urgent need to translate and widely disseminate these approaches now. To do so will necessitate critical changes in reimbursement structures, preparing the workforce in depression education, screening and nonpharmacological treatments, and helping community agencies to retool (also see Gitlin et al., 2013).

Directions for Future Research

For the promise of community- and home-based approaches to be fully realized, future research must tackle several pressing issues. First is the need for refinements in intervention delivery and specifically the development and testing of tailoring strategies of intervention protocols to match diverse cultural groups. Developing and testing strategies for systematically tailoring depression care components—such as depression education, problem solving, or behavioral activation—would enable more widespread application of these approaches. Also, it would lead to better manualization of treatments and the opportunity for diverse health and human service professionals to learn how to deliver these protocols, thus maximizing reach and adoption.

A second important area for future investigation concerns the evaluation of the performance of screening and clinical assessment tools with different racial, ethnic, linguistic, and cultural groups in various settings (agencies, home programs, church groups, senior housing) and by using diverse delivery modalities (telephone, online, web-based, teleconferencing, face-to-face in agencies, as part of in-home services such as meals on wheels) and as administered by clinicians and nonclinicians.

A third area of investigation is the dissemination and implementation of proven programs in communities, agencies, senior centers, or senior housing programs. Implementation studies are needed to determine the effectiveness of programs in real-world conditions, to study the extent of adoption and maintenance of programs in these settings, and to identify the barriers and solutions to the widespread uptake of proven programs. Finally, another area of investigation is the continual development and testing of novel delivery approaches, combinations of treatments, and the role of technologies to advance a menu of proven programs to meet the needs of highly diverse communities and agencies with varied resources.

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CHAPTER

33 Treatment of Depressive Disorders and Comorbidity in Ethnic Minority Groups

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Abstract

Depression is comorbid with anxiety, substance use, and medical conditions in majority and ethnic minority populations. Despite recognition of the growing diversity of racial and ethnic minority groups in the United States, there are significant mental health disparities among them. This chapter reviews literature on interventions of depressive disorders and other mental and medical health conditions in ethnic minority groups. It focuses on (1) the adult population, (1) treatment interventions, and (3) ethnic minority groups in the United States. This review illustrates that research on treatment of depression comorbidity is quite limited for ethnic minorities. Therefore, this chapter also discusses how cultural adaptations of evidence-based interventions for major depression can further inform the extent to which interventions for depression comorbidity can be adapted for ethnic minority populations. Research gaps, recommendations, future directions, and treatment guidelines for practitioners related to depression comorbidity and ethnic minority groups are discussed.

Key Words: depression comorbidity, anxiety, substance abuse, medical conditions, treatment, racial and ethnic minority groups, cultural adaptations

Treatment of Depressive Disorders and Comorbidity in Ethnic Minority Groups

According to the World Health Organization, major depressive disorder (MDD) will be the second leading cause of morbidity, world wide, by the year 2020 (Murray & Lopez, 1996). As reviewed in previous chapters, depression is frequently comorbid with other mental and physical conditions, with well documented adverse consequences. In addition, it is an undisputed fact that the U.S. population is increasingly diverse (U.S. Census Bureau, 2011). Ethnic minorities in the United States are projected to become the majority in the year 2042 (U.S. Census Bureau, 2008). Despite this growing diversity, there are significant mental health disparities among racial and ethnic minority and low-income groups; these groups have significant mental health problems yet have less access to quality health care and underutilize mental health services (Alegría et al., 2008; U.S. Department of Health and Human Services [U.S. DHHS], 2001). Attitudinal (e.g., stigma) and structural (e.g., financial) barriers to mental health utilization have often been cited as common reasons for not seeking mental health services (e.g., U.S. DHHS, 2001). Although there are evidence-based interventions for MDD and other mental disorders (Roth & Fonagy, 2005), ethnic minority groups have not historically been included in such efficacy studies (Bernal & Scharrón-del-Río, 2001; U.S. DHHS, 2001). This leads to the question of the extent to which the existing evidence-based interventions are applicable to ethnic minority groups and whether they need to be adapted for such groups (Bernal, Jimenez-Chafey, & Domenech Rodríguez, 2009).

This chapter reviews literature on interventions for comorbid depression and other mental and medical health conditions in ethnic minority

populations, focusing on (1) the adult population; (2) primarily treatment interventions; and (3) ethnic minority groups in the United States. We begin our discussion with the comorbidity of depression and anxiety disorders, substance use disorders, and medical conditions. These three conditions are commonly comorbid with MDD nationally and internationally and are represented by some empirical data in the three categories above. Of note, our first caveat is that the existing research on the treatment of comorbid depression and other conditions is quite limited for ethnic minority groups. Some of this research has included ethnic minority samples but does not describe how culture may affect treatment outcomes. Therefore, we also discuss cultural adaptations of interventions for MDD, a growing field that has addressed how evidence-based interventions can be adapted for ethnic minority groups, with demonstrated positive outcomes (e.g., Bernal et al., 2009; Morales & Norcross, 2010). The lessons learned from this field can further inform whether or how we can adapt interventions for depression comorbidity. Finally, we conclude by describing the research gaps, suggesting recommendations and future directions, and offering treatment guidelines for practitioners working with multicultural populations.

Comorbid Depression and Anxiety in Adults

Prevalence

There is well-documented research indicating that depression and anxiety are among the most common mental illnesses for which clients seek treatment. Indeed, comorbidity with depression and anxiety disorders is the rule rather than the exception (Kessler, Berglund, et al., 2005). To our knowledge, a few studies have examined ethnicity in comorbid depression and anxiety. This pattern of comorbidity appears not only in the United States but also generalizes to other countries, including India, Mexico, Poland, and Saudi Arabia (see review by Chentsova-Dutton & Tsai, 2009). In a sample of predominantly low-income African American and Latina women, 33% of depressed women had current comorbid posttraumatic stress disorder (PTSD) (Green et al., 2006). This rate was higher than the 17% rate reported in a predominantly White sample of depressed patients with comorbid PTSD across two sites (DeRubeis et al., 2005). In a large multisite study of depressed patients, Fava et al. (2006) found that 45% of their sample with MDD also had high levels of anxiety symptoms. Moreover, these patients—women, the unemployed, Hispanic individuals, and the less educated—were suffering from severe depression. In a study examining comorbidity of significant depressive and anxiety symptoms among Mexican immigrants, Kiang, Grzywacz, Marín, Arcury, and Quandt (2010) found that the majority had comorbid depression and anxiety (33%) as opposed to depression only (29%) and anxiety only (5%). In addition, having more daily stressors and acculturative stressors (negative experiences associated with immigrating to a new culture) increased the risk for comorbid depression and anxiety.

Consequences

Individuals with comorbid depression and anxiety carry a clinically significant economic and functional burden, tend to manifest more severe symptoms, are high consumers of health care, and are at increased risk for suicide (Fava et al., 2006; Ohayon, Shapiro, Psych, & Kennedy, 2000). For example, low-income African American women with comorbid depression and anxiety had poorer health-related quality-of-life outcomes than women with depression only or a general sample matched on age and gender (Frank, Matza, Revicki, & Chung, 2005). In a study of late-life depression in a primary care setting, women (65%) and ethnic minorities (25%) with comorbid PTSD showed a more delayed response to depression treatment than those without comorbid PTSD (Hegel et al., 2005). Furthermore, ethnic or racial minority status and comorbid anxiety disorders were significant predictors of dropouts in a study of chronically depressed patients who were randomized to either medication, cognitive behavioral analysis treatment, or combined treatments. Specifically, African Americans, Asian Americans, Hispanic people, and/or other groups were more likely to drop out of either the medication or combined treatments than did White patients.

Interventions

Interventions usually target MDD but also evaluate the impact of comorbid depression and anxiety in a subset of their depressed samples. For the most part, this research has not focused on ethnic minority populations. One exception is a study by Green et al. (2006), who reported on one-year outcomes of low-income predominantly African American and Latina women who met criteria for MDD and randomized into three types of depression treatments: cognitive behavioral therapy

(CBT), antidepressant medication, or community mental health referrals. There were no differences in response to depression treatment between African American and Latina women. Of the 267 women, 33% had depression and comorbid PTSD; these women had more serious trauma exposure, began treatment with higher levels of depression and anxiety, and had more functional impairment than did women without comorbid PTSD. The intervention was cognitive-behavioral, manualized, and included the issues pertinent to the lives of low-income women. One-year outcomes indicate that both CBT and antidepressant medication were effective in reducing depression regardless of comorbidity status. Nevertheless, women with comorbid PTSD still showed significantly more depression and worse social and role functioning over time (ranging from three months to one year post-treatment). This suggests that the residual symptoms of PTSD, anxiety, and functional impairment still need to be addressed in interventions for comorbidity.

In summary, no study has systematically evaluated the impact of culture in interventions of comorbid depression and anxiety, although the prevalence and consequences of this comorbidity are significant for ethnic minority populations.

Comorbid Depression and Substance Use Disorders

Prevalence

The comorbidity of MDD and substance use disorders (SUD) is well documented (Kessler, Chiu, Demler & Walters, 2005). In the general population, about 20% of adults with a current SUD present with at least one current independent mood disorder, and 20% of individuals with at least one current independent mood disorder have a comorbid SUD (Grant et al., 2004). African American primary care patients had a higher prevalence of comorbid MDD with lifetime diagnosis of alcohol dependence than did White patients (Brown, Schulberg, & Madonia, 1996). In a national sample of Latino adults, Vega, Canino, Cao, and Alegría (2009) found a dual diagnosis (any depressive and any anxiety disorder and any substance use disorder) prevalence rate of 6.79%. The prevalence was nearly four times higher in U.S.-born that than in foreign-born Latinos. Higher substance abuse and other psychiatric disorders in second-generation Hispanic immigrants than in more recent arrivals has been frequently reported (Alegría et al., 2007). Higher normative tolerance for substance use and the strains of the transition have been suggested as possible explanations (Substance Abuse and Mental Health Services Administration [SAMHSA], 2002; Vega et al., 2009). Other studies have also found higher rates of comorbid substance use and depressive disorders in U.S.-born White population as compared with ethnic minority groups (Kessler, Chiu, et al., 2005; Smith et al., 2006). However, this may not be the same for all ethnic groups. For example, American Indian and Alaskan Native communities have been found to have disproportionate rates of suicide, alcoholism, and illicit drug use (SAMHSA, 2002).

Consequences

People with comorbid MDD and SUD experience greater impairment than individuals with either disorder alone (Kessler, Chiu, et al., 2005; Sullivan, Fiellin, & O'Connor, 2005). Compared with those with a single disorder, those with dual diagnoses experience a higher risk of more serious substance use (Conway, Compton, Stinson, & Grant, 2006). Among those who seek treatment, individuals with both disorders also present poorer mental health and SUD treatment outcomes (Nunes & Levin, 2004) and higher treatment costs than persons who have only one disorder (SAMHSA, 2002).

Ethnic minority groups have lower rates of comorbid MDD and SUD than Whites. However, they are likely to experience worse outcomes and a greater burden as a result of the comorbid condition (Kessler, Chiu, et al., 2005). This could be because of the greater disparities in mental health services use reported for this group. They have fewer community resources available to them than Whites, and clinicians have greater difficulty connecting ethnic minorities in treatment (SAMHSA, 2002). For example, American Indians and Alaskan Native communities have disproportionately high rates of cirrhosis of the liver, accidents, violence, and intentional/unintentional overdoses related to the high rates of comorbid SUD and mental disorders (SAMHSA, 2002).

Interventions

There is evidence of important ethnic/racial disparities in mental health services utilization and access to treatment for substance use and depressive disorders (SAMHSA, 2009). Jerrell and Wilson (1997) conducted one of the most influential studies examining ethnic differences in the treatment of dual mental disorders and SUD. There were three treatment approaches: behavioral skills management, case management, and a 12-step

recovery model in a severely mentally ill (30% ethnic minority) sample. Results indicate that ethnic minority clients had lower psychosocial functioning scores and received fewer supportive treatment services during the first six months of the treatment program; however, their overall outcomes were equivalent to those of White clients at six months post-treatment. Additionally, ethnic minority clients entered the program with inadequate community support systems or with supports that they used inappropriately; they also had either limited educational background or limited work skills. All of these aspects contributed to their inability to stabilize in the community.

In a review of outpatient community 12-step participation among dually diagnosed individuals, Aase, Jason, and Robinson (2008) found that most of these studies conducted basic comparative outcomes analyses between ethnic groups. Some of the main results were (1) no differences in lifetime 12-step attendance between Hispanic and non-Hispanic Whites; (2) no association between ethnic minority status and frequency of traditional self-help group attendance; and (3) no correlation between ethnicity and attendance at a specialized 12-step program for dual diagnosis over the course of a year. The only comparison that yielded a significant difference in 12-step participation was that African Americans with dual diagnoses were more likely to attend traditional Narcotics Anonymous or Alcoholics Anonymous meetings than Whites with dual diagnoses. The authors concluded that the extent to which 12-step groups might be culturally relevant for different ethnic groups is unclear.

In a large population study on racial/ethnic disparities in service utilization for individuals with comorbid mental health and SUD, Hatzenbuehler, Keyes, Narrows, Grant, and Hasin (2008) found that individuals were more likely to use services for mood/anxiety disorders than for SUD. Compared with Whites, African Americans with comorbid mood or anxiety and SUD were significantly less likely to receive services specifically for mood or anxiety disorders, equally likely to receive services for alcohol use disorders, and more likely to receive some types of services for drug use disorders. Socioeconomic status (SES) could not completely explain these differences.

There is growing evidence that interventions for dual substance use and depressive disorders lead to improvements in both and SUD and MDD outcomes (Baker, Thornton, Hiles, Hides, & Lubman, 2011; Hobbs, Kushner, Lee, Reardon, & Maurer, 2011). Fowler, DiNitto, and Webb (2004) examined racial/ethnic differences in a sample of dually diagnosed women who received a chemical dependency treatment operated by a community mental health center and were assessed at baseline and after discharge. Results indicate that White women reported greater decreases in substance abuse and in some psychiatric domains than did ethnic minority women, suggesting the need to consider socioculturally and ethnoculturally competent treatment for all dually diagnosed women.

Tate et al. (2011) studied the predictors of treatment retention for substance-dependent adults with comorbid depression in an ethnically diverse sample (72% Whites; 28% ethnic minority, including 57.1% Blacks, 32.4% Hispanics, and 10.5% Asian/Pacific Islanders). Treatments included individual or group integrated cognitive behavior therapy (ICBT) and group 12-step facilitation (TSF) therapy. Results indicate that ethnicity was a significant predictor of attendance; on average, Whites attended 3.02 more sessions than did ethnic minorities. The authors speculate that ethnic minority individuals perceived the experiences of other group members as irrelevant to them and consequently discounted the usefulness of such treatment or that the former group feared being judged or criticized by the dominant group. The authors recommend that disparities in treatment could be reduced by creating culturally centered treatment programs or providing individually delivered interventions for members of ethnic minority groups.

An example of a culturally centered treatment approach for SUD with comorbid physical and psychological disorders has been developed for American Indians and Alaskan Natives (Gray & Nye, 2001). The Medicine Wheel is a model that addresses the individual in a holistic manner, searching for balance of the spiritual, physical, mental/emotional, and social/cultural aspects of the person. The Medicine Wheel provides a visual picture of an individual's wellness status and need for balance. The rationale for the model is that if a treatment is to be successful in achieving recovery from substance abuse, it should address the whole person holistically (e.g., its historical intergenerational trauma, all varieties of psychological pain, the quality of relationships, and education/employment). This has been proposed as being applicable to comorbid conditions associated with SUD, including depression.

In summary, research in comorbid depression and SUD suggests racial disparities in treatment

services utilization. Interventions for comorbid depression and SUD indicate that ethnic minority groups had poorer treatment outcomes than White majority groups. However, many of these studies do not include ethnic minorities in their samples; those that acknowledge inclusion do not consider the effects of this status on outcomes. For example, Watkins et al. (2011) found that a CBT intervention for comorbid depression and SUD was effective in a large ethnically diverse sample (66.2%); however, ethnic differences have not yet been explored in treatment outcomes. Indeed, very little research has been conducted on how the treatment of comorbid depression and SUD, and the results may vary based on ethnic differences. This is an area that warrants additional research.

Comorbid Depression and Medical Conditions

Prevalence

Depression is a salient mental health problem for people with medical conditions. For example, in an epidemiological study of 18 countries, chronic physical conditions were positively associated with a major depressive episode in the previous year (Kessler et al., 2010). Unfortunately certain medical conditions—such as asthma, hypertension, diabetes, HIV/AIDS, and sickle cell disease (SCD)—are disproportionately prevalent in ethnic minority populations (Gold & Wright, 2005; Liao et al., 2011). Therefore, it is important to determine whether comorbid MDD is also disproportionally present or if ethnic minority groups with medical conditions may also be at risk for the development of MDD. One epidemiologic study that focused on a Latino population with medical conditions found that 14.5% of the sample had MDD. The findings also showed that asthma was significantly associated with lifetime MDD in the entire sample, while diabetes was significantly associated with lifetime MDD only among Cuban Americans (Ortega, Feldman, Canino, Steinman, & Alegría, 2006). There is emerging evidence that the association between medical conditions and depression may be bidirectional. Namely, physical health problems may cause MDD, but likewise MDD may increase risk for certain medical conditions (Katon, 2011).

Consequences

Ethnicity, depression, and medical conditions can impact the course of treatment and health status. For example, in a study of low-income ethnically diverse patients with medical problems (common comorbidities included hypertension, arthritis, diabetes, and heart disease) and MDD, patients who were ethnic minority and young were more likely to drop out of treatment for depression (Organista, Muñoz, & Gonzalez, 1994). It has also been shown that adult African American patients with SCD and high levels of depressive symptoms were more likely to be hospitalized, to receive treatment in the emergency room, and to have blood transfusions than patients without high levels of depressive symptoms (Hasan, Hashmi, Alhassen, Lawson, & Castro, 2003). Comorbid depression has been linked with interference with diabetes self-management and self-care among ethnic minorities (Cabassa, Hansen, Palinkas, & Ell, 2008). Dysthymic mood was associated with less receipt of highly active antiretroviral therapy (HAART) by African American and Latina women with HIV compared with those without dysthymic mood as well as White men with dysthymic mood (Turner & Fleishman, 2006). Overall, some negative outcomes appear to be exacerbated by comorbidity as compared with the presence of depression only or a medical condition alone.

Interventions

The negative consequences and increased rates of comorbid depression and medical conditions indicate a need for intervention. The treatment and prevention of depression within medically ill ethnic minority populations have been identified as an understudied area of research by an expert consensus panel of the Depression and Bipolar Support Alliance (Evans et al., 2005). Although current empirical evidence is limited, interventions that focus on ethnic minority populations with comorbid depression and three medical conditions (i.e., diabetes, sickle cell disease, and HIV/AIDS) are highlighted in the following discussion.

DIABETES

Diabetes is a medical condition that has disproportionally higher rates within U.S. ethnic minority groups such as African Americans, Native Americans, and Latinos (Liao et al., 2011; U.S. DHHS, 2001). Prevalence rates of such comorbidity suggest higher rates of lifetime depression than in the general population. For example, it is estimated that depression affects 10% to 30% of individuals with diabetes (Ciechanowski, Katon, & Russo, 2000; Musselman, Betan, Larsen, & Phillips, 2003). In the Robert Wood Johnson Diabetes Initiative, 25% to 57% of patients with diabetes screened high for depressive symptoms within areas

comprising largely multicultural groups. These prevalence rates of comorbidity support interventions for this population.

An interesting development in the Robert Wood Johnson Depression Initiative is that several of the sites formed a workgroup to address the comorbidity between diabetes and depression. Owing to the diversity in the locations of these sites, many of them included ethnic minority populations. Some sites that catered to a particular ethnic/racial group incorporated cultural values into the treatment. For example, as part of the treatment for Native Americans with comorbid depression and diabetes, in addition to medication and psychotherapy, they are encouraged to attend a "talking circle" based on Native American traditions; this is utilized for additional support for patients' health and depression needs. In another example, *promotoras* (community peer coaches in Mexican cultures) provide weekly telephone contacts. They also implementd strategies for mood improvement, social support enhancement, suicide prevention, and problem solving concerning depression medication management (Anderson et al., 2007).

In another effort, the Multi-faceted Depression and Diabetes Program is a socioculturally adapted collaborative model for the treatment and management of comorbid depression and diabetes among low-income Latinos. The intervention adaptations that were culturally important included staff members who functioned as patient navigators and bilingual therapists. Additionally, problem-solving therapy was selected to be delivered based on its effectiveness with patients with diabetes and with low-income Latinos who had cancer. Pre-therapy psychoeducation, a support group, and a practice to honor the patient's first preference for treatment were patient-level cultural adaptations (Ell et al., 2009). Findings showed that depressive symptoms decreased significantly for those in the collaborative model over 24 months; however, depression differences between conditions was the most disparate at 12 months but did not differ significantly at 24-month follow-up (Ell et al., 2010, 2011). In summary, the Multi-faceted Depression and Diabetes Program showed superior benefits in the receipt of depression treatment and reduction in depressive symptoms compared with enhanced usual care. However, by 24-month follow-up, the groups were similar except that the patients in the collaborative care model were more likely to still be taking medication for depression.

sickle cell disease (scd)

SCD commonly affects people whose origins lie in Africa, India, Saudi Arabia, the Caribbean, South and Central America, and the Mediterranean (Brawley et al., 2008). In the United States, it is estimated that 1 in every 365 children born to African Americans has SCD (Hassell, 2010). There is some empirical evidence suggesting higher levels of depression in youths and adults with SCD, although this is not conclusive (Anie, 2005). A recent descriptive pilot study of African American adolescents with SCD showed that 12.5% of the sample had a lifetime diagnosis of MDD, which is higher than estimates in the general population of adolescents (Benton, Boyd, Ifeagwu, Feldtmose, & Smith-Whitley, 2011). Despite the mixed evidence of increased rates of depression among patients with SCD, the effects of living with the disease, such as episodic pain, may lead to psychological distress. In addition to empirically supported therapeutic strategies, interventions for SCD patients with depression may have to be tailored to address the unique characteristics of SCD.

In treating patients with SCD, Anie and colleagues (2002) developed a 12-session CBT intervention with a self-help manual to address physical and psychological consequences of the disease. This intervention focused on comorbid physical and psychological outcomes, including components relevant to those with depression. The intervention included patient education, cognitive restructuring, affective expression, activity scheduling, communication skills training, and relaxation techniques. In a pre-post study design, 35 adult patients with SCD participated in the intervention, although there was a 40% dropout rate. The majority (91%) of the sample from the United Kingdom were of African and Caribbean descent. The findings did not show a significant reduction in depression; however, the mean depression score on the Hospital Anxiety and Depression Scale for the sample was in the normative range. Nonetheless, there were reductions in anxiety symptoms and improvements in the quality-of-life domains of perceptions of general health and vitality. There was also a reduction in affective coping and an increase in active coping.

As part of a Comprehensive Sickle Cell Center, Comer (2004) describes the development and initial implementation of a group CBT intervention for depression for patients with SCD. Some of the guidelines for the depression group included provision of culturally and racially sensitive services, accommodating the medical needs of the patients,

and fitting within a medical setting. The group intervention supplemented general psychoeducation about depression with education about the impact of depression of physical health and SCD. Additionally, behavioral activation involved the selection and engagement of physical activities. Self-management strategies emphasized the link between mood and SCD. The participants asked to add prayer in their group, consonant with African Americans' focus on spirituality. It was found that 6 of the 10 African American participants in this pilot study showed a reduction in self-reported depression scores over 8 weeks.

HIV/AIDS

HIV/AIDS disproportionately affects African Americans (Rawlings & Masters, 2008). Additionally, the proportion of AIDS cases for Latinos in the US in 2005 was three times higher than the proportion of AIDS cases among Whites (Gonzalez, Hendriksen, Collins, Duran, & Safren, 2009). Rates of MDD among individuals with HIV range from 5–20% (Cruess et al., 2003). In a U.S. demonstration project focusing on African American and Latino adolescent males with HIV who have sex with other males, half of the participants demonstrated clinically high levels of depressive symptoms (Magnus et al., 2010). There is no strong evidence indicating that the rates of depression are more common among ethnic minorities with HIV/AIDS. Nonetheless, the increased prevalence rates of HIV/AIDS in ethnic minority women in general coupled with the higher incidence of MDD in women as compared with men has focused more attention on depression among these patients (Benton, 2008). The health disparities in prevalence rates and in the receipt of HAART also suggest consideration of interventions focused on comorbid HIV and depression for African Americans and Latinos.

A meta-analysis of eight randomized clinical trials of group therapy for individuals with HIV and depressive symptoms showed a moderate effect size (Himelhoch, Medoff, & Oyeniyi, 2007). This meta-analysis is relevant to multicultural issues in treatment as half of the U.S. studies included ethnic minority participants and one study was conducted in Hong Kong. However, no subanalyses were conducted to look at treatment effectiveness for racial/ethnic groups. Additionally, the authors commented that most of the trials were exclusively male and did not attend to the growing population of ethnic minority women with HIV.

An interesting study examined treatment by ethnicity interaction of patients with HIV and depression (Markowitz, Spielman, Sullivan, & Fishman, 2000). In the original study (Markowitz et al., 1998), participants were randomized to CBT (n = 27), interpersonal psychotherapy (IPT; n = 24), supportive therapy (n = 24), and supportive therapy with imipramine (n = 26). Depression decreased for all groups from baseline to 16 weeks post-treatment; however, IPT and supportive therapy with imipramine proved superior to the other two treatment approaches. This study was in a unique position to look at ethnicity as a result of its ethnically diverse sample (58 Whites, 21 Latinos, 18 African Americans, and 4 Asian Americans and others). The study ethnicity analyses focused on Whites, Latinos, and African Americans. The findings showed only one interaction: African Americans who received CBT had higher depressive symptoms post-treatment than did Whites and Latinos in the intervention (Markowitz et al., 2000). There was no ethnicity by treatment differences in attrition or therapeutic alliance based on an independent rater. This study needs to be interpreted with caution owing to the small sample sizes in each treatment condition. Nonetheless, it is an example of the type of intervention research that is needed to inform our practice with diverse samples with medical conditions and comorbid depression.

A pilot study to examine the feasibility of a telephone-based CBT intervention for urban African American people with HIV and depression showed promising results (Himelhoch et al., 2011). This intervention, called CONNECT, included 11 sessions focusing on behavioral activation and cognitive structuring conducted over a 14-week period. Two existing manualized cognitive behavioral interventions were tailored to address the needs of HIV-positive, depressed, individuals with more physical illness, urban residency, lower literacy, and lower socioeconomic status (SES). Six participants were included in the pre-post design pilot study. Four of the six participants completed all the sessions with a mean of nine sessions for all participants. It took three telephone calls to arrange and conduct each session. All the participants showed a decline in clinician-rated depression scores. Findings also showed high levels of participant satisfaction and patient-therapist alliance. However, this pilot study has limitations, including a small sample size, and it did not have a control group.

Another pilot intervention, ACT HEALTHY, was developed to treat depression in individuals

with HIV, depression, and substance abuse who were entering residential treatment (Daughters, Magidson, Schuster, & Safren, 2010). The 16-session intervention was developed for an urban ethnic minority population. The main focus of ACT HEALTHY is to help participants understand the cyclic relationship between activity, depressive symptoms, HIV medication adherence, and substance use. Behavioral activation is a core component of the intervention.

In summary, the interventions adapted or developed for ethnic minority groups with depression and comorbid medical conditions are emerging but limited. Culturally adapted interventions have been tested only in a randomized clinical trial for diabetes and depression, showing promising short-term findings in support of cultural adaptations. Many of the interventions presented are preliminary steps in providing treatment for multicultural populations with comorbid depression and a medical condition. These intervention strategies all include psychoeducation about the link between the medical disease and depression, provide support, and increase behavioral activation. These are based on CBT therapeutic strategies that are found effective for MDD. Although comorbid interventions appear to be indicated, the state of research in empirically supported treatments for ethnic minority groups is sparse.

Cultural Adaptations of Evidence-Based Interventions for Depression: Lessons Learned

The research above suggests that the evidence for interventions for comorbid depression and other common conditions (anxiety, substance abuse, medical illness) is limited for ethnic minority groups. Nevertheless, given the diversity of the U.S. population (U.S. Census Bureau, 2011), there is a debate about whether existing evidence-based interventions tested in majority populations are applicable for ethnic minority groups or whether such interventions should be adapted to meet the clients' cultural values and contexts in order to maximize effectiveness for this population ("multiculturalism" or "cultural adaptation" models) (Bernal et al., 2009; Morales & Norcross, 2010). Those who adhere to the latter view have examined the extent to which evidence-based treatments (EBTs) or interventions address the contextual realities of the target ethnic, racial, or cultural minority population (e.g., Aguilera, Garza, & Muñoz, 2010). Cultural adaptation is defined as "the systematic modification of an EBT protocol to consider language, culture, and context in such a way that it is compatible with the client's cultural patterns, meanings, and values" (Bernal et al., 2009, p. 262). By definition, cultural adaptation needs to take into account the dynamic culture that one is a part of (Betancourt & Lopez, 1993). To date, there are at least 11 known guides or models of cultural adaptation (D'Angelo et al., 2009; Le, Zmuda, Perry, & Muñoz, 2010) (also see review of 9 models in Zayas, Borrego, & Domenech Rodríguez, 2009). These models have several components in common. First, they all aim to identify the needs of the particular cultural group, often gathering this information through qualitative methods. Second, modifications are made to the existing evidence-based intervention, which can be surface or more in-depth modifications (Castro, Barrera, & Martinez, 2004). Third, changes to the therapeutic relationship and delivery of the intervention have been commonly addressed to increase relevance to the needs of specific cultural groups. Finally, some of the culturally adapted interventions have been tested empirically to evaluate the effectiveness of these interventions.

In general, the literature suggests that interventions that have been culturally adapted are efficacious for use with specific cultural groups. Miranda, Bernal, et al. (2005) conducted a review of psychosocial interventions for racial and ethnic minorities and found generally positive effects for the treatment and prevention of depression in African American and Latino adults. However, limited information was available for the efficacy of interventions for Asian American and American Indian populations. Griner and Smith (2006) conducted a meta-analysis of 76 studies that included various components of cultural adaptations and found a moderate effect size, suggesting that culturally adapted interventions resulted in significant client improvements across a variety of conditions and outcome measures. However, the specific type of disorder was not specified in this meta-analysis. The most frequently mentioned cultural adaptations (84% of all studies) involved explicitly including cultural values/concepts into the intervention. In particular, the authors found that interventions conducted in the clients' preferred (native) language were more effective than interventions conducted in English. Among Latinos, those who were less acculturated demonstrated a greater effect size than more acculturated participants.

Below, we describe two examples to illustrate how researchers have adapted an evidence-based intervention for major depression for Latinos. We

focus on the Latino population for several reasons: (1) Latinos are the largest ethnic minority group in the United States (U.S. Census Bureau, 2008); (2) the prevalence of MDD is increasing with each generation within the Latino group (Alegría et al., 2007; Vega et al., 1998); (3) increased rates of psychiatric disorders (depression, anxiety, substance use disorders) were found among those who were born in the United States and were English-proficient (Alegría et al., 2007); and (4) mental health disparities in access to treatment are documented in this group (Alegría et al., 2008).

In a descriptive case illustration of a culturally sensitive, evidence-based intervention, Aguilera et al. (2010) describe how they adapted a cognitive behavioral treatment for MDD with a small sample of 14 low-income Spanish-speaking Latino patients referred from their primary care providers. This case was also chosen because it included patients with a variety of comorbid diagnoses, including anxiety disorders (generalized anxiety disorder, PTSD, panic disorder) and chronic medical conditions (e.g., hypertension, diabetes, migraines). The intervention was based on a Healthy Management of Reality model (HMOR) (Muñoz, 1996) and focuses on four modules: (1) *thoughts*, increasing one's "internal reality" and cognitive restructuring; (2) *pleasant activities*, focusing on the "external reality" and behavioral activation; (3) *people contacts*, also part of the "external reality," focusing on awareness and impact of social relationships, and (4) *health*, to address the specific needs of the primary care population. Four sessions make up each module, and there are both participant and instructor manuals available (Muñoz, Ghosh Ippen, Rao, Le, & Dwyer, 2000). The manuals include graphics for those that cannot read or write English or Spanish. The cultural adaptations of this intervention focused on the delivery of the intervention, using key values endorsed by the Latino population, including a focus on *familism* ("identification and attachment of individuals with their families," p. 862), and *simpatía* (the sharing "in others' feelings while maintaining a dignity and respect toward others," p. 862). These values increased social support and social cohesion within the group. However, there were no changes in depression symptoms pre- and post-intervention. There were also some challenges in limited utilization of the treatment; 2 of the 14 participants attended only two sessions (out of 16 sessions, which is 12.5%), and the remaining group members attended an average of 60% of the sessions (ranging from 31% to 100% attendance). Additionally, there was limited adherence to completing the homework assignments. In summary, a standard CBT intervention for depression can be adapted for low-income Latinos with comorbid diagnoses, taking into account the needs of this cultural group by including relevant cultural values and education levels.

As an example of a large study, Le et al. (2010) describe a five-step iterative cultural adaptation process of a cognitive-behavioral intervention (based on the HMOR model used in Aguilera et al., 2010) for use with low-income Latinas to prevent perinatal depression in two different settings (a hospital women's clinic in San Francisco and a community primary health center in Washington, D.C.). The *Mamás y Bebés/Mothers and Babies: Mood and Health Project* began in San Francisco in 1997. The first step of their five-step model was to identify the need: Perinatal depression was chosen because this is a significant public health problem (Horowitz & Goodman, 2005), and women disadvantaged by low-income and ethnic minority status may be at higher risk (Belle & Doucet, 2003; Hobfoll, Ritter, Lavin, Hulsizer, & Cameron, 1995). Second, they gathered information through focus groups and informant interviews regarding the needs of this group within the particular context. Third, they designed the adaptation of the intervention, which follows the vast empirical work conducted by Muñoz and colleagues, using the CBT and HMOR model that was adapted for low-income primary care patients in both prevention and treatment models (Muñoz & Mendelsohn, 2005). This adaptation resulted in the a 12-week version of the *Mothers and Babies* (MB) course, which included the three core CBT modules (thoughts, pleasant activities, people contacts) and added components to address the needs and issues specific to pregnant women and new mothers as well as to the large Latina (mostly Mexican) sample; the MB course also considered intragroup cultural, racial, and linguistic differences and limited educational level. Specifically, this version provided psychoeducation on common mood problems in the postpartum period; it focused on the impact of negative mood and stressors on not only the mother-to-be but also on the upcoming mother-infant relationship. Another important addition to the MB manuals was stories that have the feel of a *telenovela*, a type of soap opera common in Latin America, making the issue of depressed mood less stigmatizing. The fourth step included the implementation,

evaluation, and refining of the adapted MB course materials. Results in the San Francisco pilot study among 41 predominantly Mexican women showed promise: at one year postpartum, 14% of women in the intervention condition developed a new onset of MDD compared with 25% of those in the usual care condition (a clinically significant difference which, however, failed to reach statistical significance). There were no differences in mean levels of depressive symptoms (Muñoz et al., 2007). The fifth step includes the replication and dissemination of this adapted MB course in Washington, D.C.

In this replication efficacy study, 217 Latinas at high risk for perinatal depression were randomized to participate in the MB course or to receive usual prenatal care (Le, Perry, & Stuart, 2011). Unlike the sample from Muñoz et al. (2007), comprising predominantly Mexican immigrants, the sample in the Washington area were predominantly from Central America, a group that was more likely to have experienced trauma in their war-torn countries (Asner-Self & Marotta, 2005). In addition, a unique risk factor of the latter group was that they had children in their home countries (Miranda, Siddique, Belin, & Kohn-Wood, 2005). These facts were incorporated into the discussion of the MB course content. Structurally, the authors also shortened the MB course from 12 to 8 weeks because most women were not able to complete these classes during pregnancy in California. The core meaning of the CBT and HMOR models was similar to that of the 12-week course, but the activities were shortened, with consultation and review from the creator (Muñoz) to reflect the most important concepts from these models. The 8-week MB course was taught in Spanish by bilingual or bicultural staff. Several efforts were made to retain participants over the 14- to 18-month study period (Le, Perry, Genovez, & Cardeli, 2012).

Results were efficacious in the short term (postintervention) but not at one year postpartum (Le et al., 2011). Participants in the intervention (INT) had significantly lower depressive symptoms than usual care (UC) participants and fewer cases of moderate depression immediately after the intervention. Depressive symptoms also decreased significantly from pregnancy to the postpartum period for women in both the INT and UC groups, but there were no differences between the two conditions at any of the three postpartum time points. The cumulative incidence of major depressive episodes was 7.8% for the women in the intervention (INT) group and 9.6% in the usual care (UC) group. Although these incidence rates were not significantly different between the experimental conditions, they are considerably lower than the rates in Muñoz et al.'s study (14% INT, 25% UC). They are also significantly lower than what would be expected in high-risk, low-income populations where rates of depressive symptoms can be as high as 50% (Administration for Children and Families, 2006), and rates of clinical depression can range from 18% to 35% (Le, Muñoz, Soto, Delucchi, & Ghosh Ippen, 2004). To further understand these differences, we conducted exit interviews with a small and randomly selected group of INT and UC participants. Qualitative analyses from these interviews revealed that the INT group, as expected, learned specific mood management skills from their participation in the prevention course, whereas the UC group experienced their participation in the study as a "low dose" intervention (Le et al., 2012).

The two examples above provide us with some lessons learned that can be applied for depression comorbidity. First, both cases are cultural adaptations of interventions that have been empirically supported for majority populations (i.e., CBT for MDD). Second, they illustrate that culturally adapted interventions can be applied for both treatment and preventive interventions. Third, there is active collaboration in the development of these interventions. For example, it is important to include bilingual and bicultural staff and participants in the development and modification of these interventions. Finally, the importance of replication and dissemination of the culturally adapted intervention is important to further determine if this can be done with a different population and context.

Gaps, Recommendations, and Future Directions

This review points to four significant gaps in the current literature for the treatment of depressive disorders and comorbidity for multicultural populations. Below, we briefly describe these gaps and provide some recommendations for future directions.

Limited Inclusion of All Ethnic Minority Groups

The disparities in access to and the quality of mental health care received by ethnic minority groups are well documented (U.S. DHHS, 2001). These disparities apply to research on one disorder as well as comorbid disorders. As reviewed above,

there is limited inclusion and attention to ethnic minority groups in the depression comorbidity treatment literature. Much more attention has focused on African Americans and Latinos than Native Americans, and none on Asian Americans. In contrast, there is somewhat better coverage in the cultural adaptation literature of single disorders for all ethnic minority groups, but there is still more research on Latinos and African Americans relative to Native Americans and Asian Americans. These findings suggest the need to attend to the specific cultural needs of all ethnic minority groups in the treatment of depression comorbidity rather than considering the impact of culture only as an afterthought. Toward this end, it is important to consider also the within-group heterogeneity of each ethnic group as well as the impact of other diversity factors, such as the intersection of culture and gender, socioeconomic status (SES), sexual orientation, identity, and disability, and how these intersections can affect outcomes as well as processes of interventions for depression comorbidity.

Limited Attention to Prevention

The above review also suggests that the current state of research in depression comorbidity has largely focused on treatment. Much less attention has been paid to the prevention of depression comorbidity despite the fact that subclinical rates of depression can result in negative mental health consequences as compared with clinical depression (Cuijpers, de Graaf, & Van Dorsselaer, 2004). Effective prevention programs may reduce the enormous burden of mental disorders (Jané-Llopis, Hosman, Jenkins, & Anderson, 2003), which account for 22% of the total burden of disease; moreover, the most common mental disorders (depression, anxiety, and SUD) account for three quarters of the burden of all mental disorders (Murray & Lopez, 1996). However, treatment methods can reduce only an estimated half of the burden of the common mental disorders (Andrews & Wilkinson, 2002). Therefore, it is critical to focus on research to evaluate interventions to prevent depression comorbidity. Cuijpers, Van Straten, and Smit (2005) conducted a meta-analysis of 13 randomized controlled trials aimed at preventing several conditions, including depression, anxiety, psychosis, any mental disorder, and comorbid depression and anxiety in youth. Results from the meta-analysis indicate that "preventive interventions are capable of reducing the incidence of mental disorders. This effect seems to be especially clear in cognitive behavioral interventions aimed at depressive and anxiety disorders. In the examined populations, approximately 12% to 19% of the new cases are prevented" (p. 123). These findings provide some optimism and guidance to further develop and evaluate interventions aimed at the prevention of depression and comorbid conditions.

Limited Attention to Children and Adolescents

By default, our chapter focuses on adults because there was a paucity of research on treatments for comorbid depression and other conditions in children and adolescents. As in adults, depression is commonly comorbid with anxiety, substance abuse, and selected medical conditions (e.g., asthma, SCD) in children and adolescents (Armstrong & Costello, 2002; Benton et al., 2011; Garber & Weersing, 2010; Katon et al., 2007). Nevertheless, the field is behind in this population and even more so for ethnic minority youth. This is an important area of study because youth who exhibit depression are at risk for MDD in adulthood (Weissman et al., 1999). Several interventions aimed at MDD in youth have been shown to reduce depressive symptoms (March et al., 2007; Mufson et al., 2004). A meta-analysis of therapeutic interventions for children and adolescents with depression demonstrated that anxiety symptoms are also reduced (Weisz, McCarty, & Valeri, 2006), suggesting that current interventions may be helpful with comorbid symptoms. Some of these interventions were adapted for or empirically tested with ethnic minority youth with depression (Rosselló, Bernal, & Rivera-Medina, 2008; Yu & Seligman, 2002). A few intervention studies were aimed at depression with other comorbid conditions in youth; an example is CBT with depression and inflammatory bowel disease (Szigethy et al., 2007). Based on the current state of the science, we cannot draw any conclusions about depression and comorbid conditions among ethnic minority children and adolescents. This area represents a significant gap in research and intervention models, and interventions are needed to address the mental health needs of these youth.

Limited Use of Technology in Interventions with Ethnic Minorities

Web-based interventions for the psychological treatment of different mental conditions are a rapidly developing field. Their accessibility, lower cost, and potential to diminish the stigma associated with mental problems make these interventions particularly attractive. They can be used as

alternatives to or in conjunction with in-person interventions. Randomized controlled studies indicate that they are efficacious in treating comorbid disorders such as depression and anxiety (Griffiths, Farrer, & Christensen, 2010), depression and SUD (Kay-Lambkin, Baker, Lewin & Carr, 2008), and depression and diabetes (Van Bastelaar, Pouwer, Cuijpers, Riper, & Snoek, 2011). Internet interventions also provide an opportunity for innovative, culturally sensitive interventions for treating co-occurring conditions for ethnic minorities. Muñoz et al. (2009) reported that a web-based program for smoking cessation and mood adapted for English- and Spanish-language groups is feasible and effective (significantly increasing smoking quit rates) for ethnically diverse populations.

Mobile applications also offer the possibility of improving the cost-effectiveness of treatment for mental disorders. Mobile technology can play a role in managing noncritical care within the community by reducing relapses, thus improving patients' quality of life (Agyapong, Ahern, McLoughlin, & Farren, 2012). Agyapong et al. (2012) explored the effects of supportive text messaging on mood and alcohol abstinence in patients with MDD and comorbid SUD following discharge from an inpatient dual diagnosis program. Results from this randomized rater-blinded trial indicate a significant reduction in depression and a trend toward greater abstinence in the group that received text messages as compared with a control condition. In CBT groups with a Spanish-speaking sample with comorbid MDD and various psychological and physical conditions, audio coaching (uploaded onto mp3 players) and cell phone–based text messaging were used as a means to enhance adherence and to increase the dosage of treatment (Aguilera et al., 2010). This study found that patients responded well to these devices, using the mp3 player an average of three to five times per week. These devices have multiple functions, including collecting continuous data, providing feedback, and giving coaching throughout the day. Overall, these examples suggest that mobile phone technology holds promise in providing cost-effective, culturally sensitive interventions for comorbid depression and other conditions.

Treatment Guidelines

In this section, we provide some treatment guidelines for practitioners who are working with multicultural clients with MDD and comorbid conditions. Multiple proponents and professional organizations have created mandates to increase cultural competency to effectively work with ethnically diverse populations (American Psychological Association [APA], 2003, 2006; Sue, Zane, Hall, & Berger, 2009). The Presidential Task Force on evidence-based practice of the APA (2006) defines *Evidence-Based Practice in Psychology* (EBPP) as "the integration of the best available research with clinical expertise in the context of patient characteristics, culture, and preferences" (p. 273). As reviewed above, the "best research evidence" is still quite limited for comorbid depression and other physical and psychological disorders. Therefore, clinicians must use their clinical expertise to develop competencies that promote positive therapeutic outcomes—that is, by "understanding the influence of individual, cultural, and contextual differences on treatment, including but not limited to age and development, ethnicity, culture, race, gender, sexual orientation, religious commitments, and SES" (p. 277). Within this context, we provide treatment guidelines for practitioners in three areas: assessment, treatment, and prevention. These guidelines pertain to all disorders, whether single or comorbid disorders, psychological or medical conditions; they are still works in progress.

Assessment

It is well documented that the experience and expression of depression can vary cross-culturally (for a review, see Chentsova-Dutton & Tsai, 2009). In general, ethnic minority and nonwestern groups are more likely to emphasize somatic and less likely to emphasize psychological symptoms of depression relative to European-American groups. There are also culture-specific idioms of distress (e.g., fatigue and "imbalance" in Asian cultures) (American Psychiatric Association, 2000). Furthermore, ethnic minority clients are less likely to dichotomize the mind-body relationship. It is likely that these factors influence the experience and expression of other physical and mental disorders that are comorbid with depression. Thus, all of these factors suggest that practitioners need to do a careful assessment of how depression and comorbid physical and other mental health conditions are conceptualized and expressed in diverse cultural groups in clinical settings.

Treatment

It is important for practitioners to determine what disorder to treat first: the depression or its comorbid condition. How does the individual's culture view the importance of these conditions? "Cultural factors, such as fatalism, acceptance of suffering,

stigma, and cultural conceptions of depression as being interpersonally based. . . (Chentsova-Dutton & Tsai, 2009, p. 379)" may contribute to both low rates of treatment seeking and high rates of dropouts from treatment. For example, ethnic or racial minority status and comorbid anxiety disorders were significant predictors of dropouts in a study of chronically depressed patients (Hegel et al., 2005). Therefore, it is important for therapists to gain an in-depth understanding of their own and the client's cultural heritage, identity, and values (APA 2003, 2006), which can help increase retention in therapy and improve therapeutic outcomes. For example, Kaslow and colleagues (2010) evaluated the efficacy of a culturally informed, empowerment-focused psychoeducational group intervention for low-income (45.2% homeless) African American women who were experiencing comorbid interpersonal partner violence (IPV) and suicide attempts. This culturally adapted intervention resulted in decreased depressive symptoms and less severe suicidal ideation among such patients when exposed to physical or nonphysical violence than among the treatment-as-usual group.

Some researchers have advocated matching clients and therapists on the basis of culture, race, and language; this has been shown to strengthen the therapeutic alliance, reduce attrition, maximize treatment adherence, and enhance identity development and modeling (Sue & Sue, 1999). Interventions conducted in the client's preferred (native) language were found to be more effective than interventions conducted in English (Griner & Smith, 2006). However, the reality is that the number of available ethnic practitioners is significantly lower than the number of ethnic clients in need (Ruiz, 2002). Therefore, it is more important to develop cultural competency or a "culture centered" approach in working with diverse ethnic groups (APA, 2003, 2006; Sue et al., 2009).

As mentioned above, the use of internet interventions and mobile technology can be effective in treating MDD and comorbid disorders. Clinicians should assess whether these tools can serve as adjuncts to individual treatment or as alternatives to in-person treatments for these conditions. Combined with the use of e-mails and brief telephone calls with a clinician, cell phone and internet interventions may be potent, appealing devices to reduce barriers to treatment of ethnically diverse populations.

Finally, it is important to consider the role of alternative or indigenous treatments in working with multicultural clients; these can be relevant to treatment adherence and may increase the effectiveness of treatment. For example, Gray and Nye (2001) discussed the inclusion of the Medicine Wheel in working with American Indians and Alaskan Natives who present with SUD and comorbid physical and psychological disorders, proposing that this can be a model that would work for depression and comorbid conditions. In addition, meditation, mindfulness practices, and yoga have been found to be effective in treating depression (Segal, Williams, & Teasdale, 2002; Woolery, Myers, Sternlieb, & Zeltzer, 2004). These practices can be further explored to determine whether they would also be effective as adjunctive treatments for the comorbid medical and psychological conditions associated with depression in multicultural populations.

Prevention

Prevention efforts for depression and comorbid conditions are warranted for ethnic minority populations. Selective prevention is aimed at individuals who exhibit risk factors for MDD, while indicated prevention is aimed at individuals exhibiting high levels of depressive symptoms (Mrazek & Haggerty, 1994). These types of prevention may be less stigmatizing and more acceptable to ethnic minority populations, especially if disorder is not the emphasis. In addition, these types of preventive interventions can be implemented in non–mental health settings, thus increasing the accessibility to larger samples of individuals. For example, the *Mothers and Babies* course demonstrates a successful preventive intervention aimed at MDD; it has been shown to be effective with ethnic minority women (Le et al., 2011). These prevention efforts open up wide possibilities for implementation in real-world settings.

Another important aspect of treatment is the prevention of relapse. Once an individual with comorbid depression achieves remission, it is critical to involve strategies to prevent the major depressive episode from returning. If an individual drops out of treatment prematurely, as is commonly the experience with ethnic minority groups, then he or she is at risk for relapse. A plan for relapse prevention should be developed during the course of treatment which would include the client as well as other important people in the client's life. The clinician's goal is to implement a relapse prevention plan that will be effective once the client's depression and possibly comorbid conditions are in remission. This could involve booster sessions that could be conducted at larger intervals of time than treatment. With clients who are in

therapy, it is important to have the therapist assess for the clients' skills development and ability to use these skills on their own in order to prevent relapse. Securing support systems for the clients can be important (Segal, Pearson, & Thase, 2003; SAMHSA, 2009), especially with ethnic minority groups in which family and community relationships are important cultural values.

Conclusion

The comorbidity of depression and common psychological and medical conditions is prevalent. Moreover, the growing diversity of populations in the United States is undisputed. However, the current field on interventions for adults with comorbid depressive disorders and common psychological and medical conditions does not reflect this growing diversity and is quite limited for ethnic minority groups. In contrast, there is a growing field of research addressing how evidence-based interventions for a single disorder, such as MDD, can be successfully adapted for ethnic minority populations. There is a critical need to marry these two disparate but related fields of research so that they can further inform each other on how interventions for depression comorbidity can be culturally adapted for ethnic minority groups. Both researchers and practitioners can benefit from this marriage to provide the most effective preventive and treatment services for ethnic minority groups.

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CHAPTER

34 Psychosocial Interventions for Depressed Breast Cancer Patients

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Abstract

Clinical depression affects many people and is associated with several risk factors that include being diagnosed with a serious medical illness such as breast cancer. Objectives of this chapter were to elucidate the prevalence of depression in breast cancer patients, the impact of depression as it pertains to life functioning and quality of life, highlight the bidirectional relationship of breast cancer and depression, outline assessment strategies and measurement issues relevant to assessing depression, and review the treatment outcome literature addressing the efficacy of psychosocial interventions for depressed breast cancer patients. Depression is highly prevalent among breast cancer patients, significantly impacts life functioning, may be associated with cancer progression and mortality, and is bidirectionally related to breast cancer through several pathways. Many behavioral assessment strategies may be useful for recognizing depression in breast cancer patients, and, although methodological weaknesses are evident, several psychosocial interventions show substantial promise as effective treatments for depressed breast cancer patients.

Key Words: psychosocial treatment, depression, breast cancer, review

Among cancer patients, major depressive disorder (MDD) is the most common psychiatric disorder, with prevalence rates differing as a function of cancer location. The highest prevalence rates occur in patients with oropharyngeal (22–57%), pancreatic (33–50%), breast (20–46%), and lung cancers (15–44%), but also fairly commonly in colon (13–25%), gynecological (12–23%), and lymphoma (10–19%) (Croyle & Rowland, 2003; Fann et al., 2008; Massie 2004). In the past several decades, accumulating research has examined the efficacy and effectiveness of psychological interventions for depressed cancer patients, and, perhaps most extensively, the adequacy of these treatments for women with breast cancer. The objective of this chapter is to highlight the relationship between depression and the experience of being diagnosed and living with breast cancer. Following a brief overview of the prevalence and impact of MDD and its risk factors, the central aims will be to discuss the prevalence and impact of depression as it pertains to life functioning and overt behaviors of breast cancer patients, examine theories surrounding the bidirectional relationship of breast cancer and depression, review assessment strategies relevant to identifying MDD in breast cancer patients, and present a comprehensive analysis of treatment outcome studies on breast cancer patients with depression, including discussion of limitations and future directions that need to be addressed to improve methodological shortcomings of treatment outcome research and quality of care for women with breast cancer and MDD.

Prevalence, Impact, and Risk Factors for Depression

Results of the National Comorbidity Survey suggest a lifetime prevalence of 16% for MDD (NCS-R: Kessler et al., 2003) and in medical care

settings, as many as 25–30% of patients present with MDD (Wittchen et al., 2000; Wolf & Hopko, 2008). MDD is associated with considerable morbidity, mortality, and quality of life decrements through multiple pathways (Cuijupers & Smit, 2002; Herrman et al., 2002; McGirr & Turecki, 2007; Mokdad et al., 2004; Musselman, Evans, & Nemeroff, 1998; Satin, Linden, & Phillips, 2009; Segrin, 2000). Depression also is related to negative health behaviors that include weight gain (Strine et al., 2008), smoking (Fiore et al., 2008; Pratt & Brody, 2010), substance use (Sullivan, Fiellin, & O'Connor, 2005), and noncompliance with medical regimens (DiMatteo et al. 2000). In addition, the economic costs of treating MDD are staggering (Crown et al., 2002; Greenberg et al., 2003). A number of risk factors are linked to the development, persistence, and severity of MDD. These factors include female gender, marital separation or divorce, unemployment, exposure to trauma, physical and sexual abuse, other stressful and adverse life events, maladaptive cognitive styles, dispositional pessimism, family history of depression, insecure parental attachments, genetic predispositions, hormonal influences, neurochemical processes, poor physical health and medical illness, functional limitations, lower socioeconomic status, poor social support, behavioral avoidance, and limited coping skills and problem-solving abilities (Dobson & Dozois, 2008; Klein & Santiago, 2003; Hopko, Lejuez, Ruggiero, & Eifert, 2003; Lorant, Croux et al., 2007; Mazure & Keita, 2006; Person, Tracy, & Galea, 2006; Spasojevic & Alloy, 2001). Taking these factors into account, many psychological theories have conceptualized the etiology, maintenance, and severity of MDD, most also addressing important gender differences in the onset of MDD (Corveleyn, Luyten, & Blatt, 2005; Dobson & Dozois, 2008; Gotlib & Hammen, 2009).

Gender Differences in Depression

Females are more likely to have internalizing disorders such as depression and anxiety (APA, 2000; Barlow, 2002), and men have a higher prevalence of externalizing disorders, including antisocial personality disorder and substance abuse (Brady & Randall, 1999; Rosenfeld, 2000). In terms of MDD, research indicates depression is more common among females (21%) than males (13%; APA, 2000; Kessler et al., 2003). Biological factors such as hormones, adrenal functioning, and neurotransmitter systems, and psychosocial influences including aversive childhood experiences, gender role stress, vulnerability to emotional pain of others, and differential attributions contribute to this gender difference (Dobson & Dozois, 2008; Freeman et al., 2004; Nolen-Hoeksema & Hilt, 2009; Piccinelli & Wilkinson, 2000; Steiner, Dunn, & Born, 2003). Females also are more likely to ruminate, exacerbating distress in response to stressful experiences (Nolen-Hoeksema, 1994; Nolen-Hoeksema & Hilt, 2009).

Breast Cancer and Depression

Prevalence

Although recent data suggest the incidence of breast cancer has remained relatively stable in the past decade (Eheman et al., 2012), in the upcoming year approximately 226,000 new cases of invasive breast cancer will be diagnosed among women in the United States (American Cancer Society, 2012). A breast cancer diagnosis can be traumatic and elicit emotional experiences ranging from depression, anxiety, and anger, including *physiological* (autonomic nervous system arousal), *cognitive* (sense of hopelessness, helplessness, foreshortened future, negative attributions), and *behavioral* reactions (social withdrawal, lethargy, substance use). Along with substantial variability in reacting to a breast cancer diagnosis, patients exhibit significant differences with respect to the frequency and intensity of concurrent life stressors, degree of social support and other coping resources, vulnerability to mental illness, and the extent to which other risk factors affect the likelihood of developing a psychiatric disorder. Breast cancer patients also are differentiated with regard to malignancy type, cancer stage, and associated prognosis.

In the context that roughly 20–46% of breast cancer patients develop MDD (Croyle & Rowland, 2003; Fann et al., 2008; Massie 2004), understanding the many potential psychological and biological explanations for depression and gender differences in depression is even more complicated in the context of a medical illness such as cancer. Two of the more obvious questions pertain to whether individuals with cancer experience roughly equivalent prevalence rates and similar gender differences in depression relative to those without cancer. To address the first question, an influential study examining depression prevalence via structured clinical interviews determined that roughly 53% of cancer patients adjusted "normally" to cancer-related stress whereas 47% had clinically significant psychiatric problems (Derogatis, Morrow, & Fetting, 1983). Within this latter group, approximately two-thirds

had adjustment disorders with depressed mood and 13% had MDD, with 90% of the disorders believed to be reactions to or manifestations of disease or treatment. In another early investigation, six-month and lifetime prevalence rates of psychiatric disorders were higher in those with chronic medical illness (25% and 42% versus 17% and 33%) and 13% of the chronically medically ill had a lifetime diagnosis of a mood disorder compared to 8% without a chronic medical illness (Wells, Golding, & Burham, 1988). Important to acknowledge, rates of depressive states for cancer patients are roughly comparable to similarly ill patients with other medical diagnoses (Evans et al., 2005). Collectively, it is clear that MDD and adjustment disorders are significant psychiatric problems in cancer patients that, in large part, may be triggered by the diagnosis and subsequent cancer treatment. Important to highlight, however, although MDD prevalence rates in cancer patients may be higher than the general population (Van't Spijker, Trijsburg, & Duivenvoorden, 1997), some suggest MDD is equally common in cancer patients and control groups, and this issue is far from resolved (Lansky et al., 1985; cf. Massie et al., 2004). Among the many reasons for equivocal data is inadequate standardization of populations studied, small sample sizes, inadequate control of cancer site and stage, differential assessment instruments, cutoff scores, type of clinical interview, and disparate diagnostic criteria (e.g., MDD, dysthymia, adjustment disorder with depressed mood, depressive symptoms) (Massie, 2004). Moreover, a valid diagnosis of MDD is made even more difficult due to considerable overlap of depressive and medical symptoms observed in cancer patients (Table 34.1; Raison & Miller, 2003). Consistent with difficulties ascertaining more precise MDD prevalence rates in cancer patients, there is a paucity of research on potential gender differences in cancer patients with depression. In a review on this very issue, research studies on gender differences in cancer-related depression, pain, and fatigue are not only minimal in number, but they are also restricted to studies of differences in prevalence rates and severity scores, have generally not included structured diagnostic strategies, and have, for the most part, yielded conflicting results (Miaskowski, 2004). One encouraging finding is that prevalence rates of MDD in cancer patients appears to be decreasing in the past few decades, which may reflect improved cancer treatments, better medical outcomes, and improved social support resources for cancer patients (Kissane, Maj, & Sartorius, 2011; Spiegel & Giese-Davis, 2003). Important to note, the prevalence rates of MDD in children, the elderly, and minority individuals with cancer are largely understudied (Evans et al., 2005; Hopko, Colman, & Carvalho, 2008; Massie, 2004).

Although MDD prevalence rates in cancer patients are substantial, the majority of individuals diagnosed with cancer are not in fact concurrently depressed. Beyond typical risk factors outlined earlier, several cancer-specific risk factors are associated with the likelihood of developing MDD. First, as cancer disease severity increases (i.e. higher stage), so does the frequency of co-existent depressive conditions (Ciaramella & Poli, 2001). Second, certain components of cancer treatment may increase the odds of developing depression (cf. Raison & Miller, 2003), including cytokine development and cancer-related medications (Capuron et al., 2002), certain chemotherapy regimens and chemotherapeutic interventions during childhood (Zebrack et al., 2002), and although a controversial issue, possibly surgical procedures such as breast mastectomies (Massie, 2004; Omne-Ponten, Holmberg, Burns, Adami, & Bergstrom, 1992). Third, duration of time elapsed since cancer diagnosis also may impact prevalence rate, with cancer patients generally more vulnerable to developing depression in the year following cancer diagnosis (Honda & Goodwin, 2004), particularly if they have a history of depression (Kissane et al., 1998). In a longitudinal study of women diagnosed with breast cancer, approximately 50% of the women met diagnostic criteria for depression in the year immediately following diagnosis, 25% in the second, third, an fourth years, and approximately 15% in the fifth year (Burgess et al., 2005). Among patients with either head and neck cancer or lung cancer, approximately 29% were depressed at 1-month post cancer diagnosis and roughly 20% remained depressed at 12-months post-diagnosis (Kangas, Henry, & Bryant, 2005). Fourth, a number of psychosocial variables may increase the likelihood of a cancer patient developing depression, including being single, having more children, decreased social support, substance abuse, decreased religiosity, unemployment, and co-existent medical problems (Deshields, Tibbs, Fan, & Taylor, 2006; Zabora, Brintzenhofeszoc, Curbow, Hooker, & Piantadosi, 2001). Breast cancer patients also are more likely to develop MDD if they have poor family cohesion and increased family conflict, maladaptive problem solving skills, and the presence of pain and fatigue (Lueboonthavatchai, 2007).

The Impact of Depression in Breast Cancer Patients

Clinical depression can greatly impact the functioning of breast cancer patients and a variety of cancer-related symptoms may in turn be exacerbated by depression. In a recent literature review, out of 24 studies that assessed whether depression was linked with cancer progression, over 60% reported positive associations (Spiegel & Giese-Davis, 2003). For example, the co-occurrence of depression with cancer may be related to increased pain and other physical symptoms. Breast cancer patients with depression often experience more intense pain and have a greater prevalence of metastasis than nondepressed cancer patients (Aukst-Margetić et al., 2005; Chen & Chang, 2004; Ciaramella & Poli, 2001; Hopko et al., 2008; Mystakidou et al., 2007). Among breast cancer patients, strong associations between depression symptoms and physical symptoms of pain, respiratory distress, and fatigue also have been observed (Lueboonthavatchai, 2007). It is important to note that the relationship between depression and physical pain is bidirectional, with pain potentially associated with the etiology and maintenance of depression symptoms, and negative affect functioning to intensify pain experiences. For breast cancer patients, including those with metastatic cancer, there are some encouraging data suggesting cognitive-behavioral therapy, supportive therapy, and hypnosis may significantly reduce pain symptoms, as well as symptoms of nausea and vomitting (Butler et al., 2009; Enqvist et al., 1997; Montgomery et al., 2007; Tatrow & Montgomery, 2006). Moreover, there also appear to be substantial benefits for breast cancer patients receiving mindfulness-based stress reduction relative to patients receiving no treatment on other physiological outcomes, including reduced blood pressure, heart rate, and respiratory rate (Matchim, Armer, & Stuart, 2011).

The most serious correlate of depression in breast cancer patients is its potential impact on mortality. Although multiple studies have not supported a relationship between depression and breast cancer progression or mortality (Bleiker et al., 1996; Tross et al., 1996; Zonderman, Costa, & McCrae, 1989), an equally significant body of research in the past decade has supported this link (Satin et al., 2009). For example, in an important prospective study, the impact of depression on cancer incidence and mortality was examined in a sample of 4,825 cancer patients over the age of 71. In addition to depression being associated with an 88% increased likelihood of developing cancer, chronically depressed cancer patients were nearly twice as likely to die over a 4-year follow-up relative to nondepressed patients (7.5% compared to 4.1%: Penninx et al., 1998). In a retrospective study, Goodwin, Zhang, and Ostir (2004) reported that older women with breast cancer had a significantly higher risk of mortality if they had been diagnosed with depression within the past two years, even after controlling for age, ethnicity, and comorbidity. In a third study that prospectively studied 578 women with early-stage breast cancer, helplessness, hopelessness, and depression were related to a significantly reduced chance of survival (Watson et al., 1999). In a recent meta-analysis examining 25 independent studies, mortality rates were up to 25% higher in cancer patients with depressive symptoms and up to 39% higher in patients diagnosed with major or minor depression (Satin et al., 2009). In addition to these studies, several others highlight a possible relationship between depression and breast cancer mortality rate (Hjerl et al., 2003; Hoodin et al., 2004), and it is highly feasible that breast cancer patients with MDD may have greater aspiration for euthanasia or physician-assisted suicide (Emanuel, Fairclough, & Emanuel, 2000; Wilson et al., 2007).

Another significant impact of depression involves decreased quality of life among breast cancer patients (Frick, Tyroller, & Panzer, 2007; Ganz et al., 2003). Quality of life refers to an individual's sense of well-being across various life domains, including physical and psychological functioning, social relationships, and spirituality. Problems in the realms of social support, self-care, recreation, family stress, mobility, physical activities, employment status, and sleep are all related to depression and decreased quality of life in breast cancer patients (Hopko et al., 2008; Mellon, Northouse, & Weiss, 2006; Mystakidou et al., 2007; Parker et al., 2003; Shukla, et al., 1999). Some demographic and clinical variables also are related to depression and decreased quality of life, including being single, female, less educated, and having more advanced cancer (Parker et al., 2003). In a recent study comparing depressed and nondepressed (primarily) breast cancer patients, Hopko et al. (2008) reported that depressed patients indicated a poorer quality of life, increased anxiety and bodily pain, and decreased vitality and social functioning. In a study comparing women with malignant breast cancer to those with benign tumors, depression was associated with decreased quality of life in both groups, and among those with cancer, illness stress

was the most robust predictor of life satisfaction (Yen et al., 2006).

The comorbidity of depression and breast cancer can also have a dramatic effect on the costs of health care, utilization of medical services, and overall burden on the health-care industry. A large scale study of elderly Medicare beneficiaries with severe and chronic medical illnesses, including breast cancer, who also met criteria for MDD were at least twice as likely as those without MDD to utilize emergency department services, medical inpatient hospital services, and inpatient hospital services associated with ambulatory care conditions (Himelhoch et al., 2004). Oleske et al. (2004) reported that depression symptomatology accounted for unique variance in predicting the frequency of overnight hospitalizations among women with breast cancer. Importantly, research suggests early detection of depression and other indications of general distress in cancer patients may help improve treatment outcome and reduce the costs of health care (Zabora et al., 2001).

Depression and Breast Cancer: A Bidirectional Relationship

The comorbidity of depression and breast cancer is substantial, and the causal relationship between this psychiatric and medical problem is inherently bidirectional. It is strikingly evident that comorbid depression and breast cancer is associated with increased functional impairment and decreased quality of life (Hopko et al., 2008, 2011; Kissane et al., 2011). Therefore, understanding linkages between conditions is critical toward case conceptualization, minimizing their synergistic effects, and facilitating positive treatment outcome. First, insofar as breast cancer is causally related to the etiology and maintenance of depression, the very experience of being diagnosed and living with breast cancer is a stressful life occurrence that may trigger a depressive episode, particularly among women with a biological diathesis or vulnerability to depression (Kissane et al., 2011; Schotte, Van Den Bossche, De Doncker, Claes, & Cosyns, 2006). Second, in addition to the existential stress of living with breast cancer, the likelihood of developing depression is related to more severe and rapidly progressing cancer symptoms such as pain (Ciaramella & Poli, 2001; Spiegel, Sands, & Koopman, 1994). Third, it has been proposed that depression may be directly related to antineoplastic therapy and radiation treatment, as well as treatment side effects such as nausea, vomiting, and hair loss (Brown, Levy, Rosberger, & Edgar, 2003; Capuron et al., 2002; Evans et al., 2005; Raison & Miller, 2003). In fact, one group of researchers demonstrated that as many as 50% of patients receiving chronic, high dose, interferon-α-2-β therapy develop MDD (Musselman et al., 2001). Finally, it should be noted that although some surgical procedures (e.g., mastectomies) and related consequences (e.g., problems with body image) have been associated with an increased likelihood of developing depression (Omne-Ponten et al., 1992), many studies have not elucidated such a relationship (cf. Raison & Miller, 2003).

Although depression may be an emotional consequence of being diagnosed and treated for breast cancer, there are some good data suggesting depression may also function as a causal risk factor for cancer diagnosis and progression, with evidence generally stronger for the depression and cancer progression relationship (Spiegel & Giese-Davis, 2003). First, in addition to illness-related stress highlighted earlier, an accumulation of life stressors and possible psychological distress may increase breast cancer risk. For example, Lillberg and colleagues (2003) reported that, in a large sample of women, a greater number of stressful life events during a 5-year period before baseline assessment was associated with an increased risk of breast cancer at 15-year follow-up. Second, depression may be associated with fewer benefits and poorer recovery from breast cancer treatment because depression is linked with reduced optimism about the effects of medical interventions and poorer adherence to breast cancer treatment regimens and screening procedures (Cohen, de Moor, & Amato, 2001; Evans et al., 2005; Lerman et al., 1994; Somerset, Stout, Miller, & Musselman, 2004). Third, as highlighted in the previous section, depression and associated negative cognitions (e.g., hopelessness, negative attributional style, tendency to overcontrol and suppress emotions) appear related to increased breast cancer incidence, progression, and mortality (Goodwin et al., 2004; Hjerl, Andersen et al., 2003; Stommel et al., 2002; Penninx et al., 1998), although some studies have not supported these findings (cf. Spiegel & Giese-Davis, 2003). Fortunately, although depression may be associated with increased mortality and with the concession that data are highly inconclusive and controversial (Goodwin et al., 2001; Kissane & Li, 2008; Kissane et al., 2011), there are at least a few studies suggesting that depressed breast cancer patients who undergo psychotherapy may have

prolonged survival times (e.g., Spiegel et al., 1989, 2007; Somerset et al., 2004).

Finally, from a biological functioning perspective, depression may be related to the etiology and progression of breast cancer through various endocrine system functions. For example, disruption of circadian cortisol rhythms and elevated cortisol levels are not only linked with depression, but also may be typical among breast cancer patients (Touitou et al., 1995) and potentially associated with earlier mortality (Sephton et al., 2000). Increased cortisol levels also have been associated with decreased immune system functioning and possibly increased tumor growth [see Spiegel & Giese-Davis (2003) for a review of this literature]. Moreover, there is accumulating evidence that cancer, fatigue, pain, and depression share a common biological mechanism, namely increased levels of proinflammatory cytokines [e.g., interleukin (IL)-1, IL-6, C-reactive protein (CRP), tumor necrosis factor (TNFR1 & R2), and interferon-Alpha (IFN-Alpha)]. In response to disease, infection or tissue damage, and cancer treatment, cytokines and chemokines are produced by the immuno-inflammatory system. The association between breast cancer and depression is in part due to activation of the immuno-inflammatory systems and associated dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis (Belmaker & Agam, 2008), marked by increases in circulating proinflammatory cytokines like Interleukin (IL)-6, TNF, and CRP (Dantzer & Kelley, 2007; Miller, Maletic, & Raison, 2009). Individuals with MDD exhibit increased proinflammatory cytokines, secreted acutely in response to infection as well as acute and chronic psychological stress (Kiecolt-Glaser et al., 2003; Steptoe, Wardle, & Marmot, 2005). Chronically high levels of cytokines are linked to increased severity of depression and diagnosable MDD (Howren, Lamkin, & Suls, 2009; Raison, Capuron, & Miller, 2006). Administration of interferon-alpha, and subsequent induction of "immune-induced depression" in patients with malignant melanoma has confirmed perturbation of pathways relevant to mood regulation, that is, the HPA axis and CNS metabolism of serotonin and dopamine (Bower et al., 2002; Musselman et al., 2001; Raison et al., 2006). Given their strong associations with breast cancer and depression, assessment of cytokines and signaling pathways represent a novel approach to assess the efficacy of interventions for breast cancer and depression (Capuron et al., 2003; Howren et al., 2009; Raison et al., 2006). Consistent with theory that increased cytokine production is associated with both cancer and MDD, antidepressant therapy seems to not only effectively attenuate depressive symptoms, but also reduce elevated cytokine plasma levels in cancer patients (Capuron et al., 2002; Musselman et al., 2001). At this stage of research, there are no outcome studies evaluating the potential effects of psychosocial interventions for depression on cytokine plasma levels.

Assessment and Screening of Depression in Breast Cancer Patients

The importance of early detection of both breast cancer and MDD is highly documented. For example, the diagnosis and treatment of breast cancer in its early stages is associated with a 5-year survival rate of approximately 90% (ACS, 2012). Similarly, although early detection of MDD in breast cancer patients can improve quality of life and possibly reduce the progression of cancer and associated mortality rates (Kissane et al., 2011; Spiegel & Giese-Davis, 2003), research indicates depression may be highly underdiagnosed and undertreated in breast cancer patients, partially due to perceptions that depression is a normal and predictable reaction to having a serious medical illness such as breast cancer (Fann et al., 2008; Spiegel & Giese-Davis, 2003). Underrecognition also is at least partially associated with symptom overlap among breast cancer treatment and depressive symptoms (Bailey et al., 2005), including sleep disturbance, weight loss, psychomotor retardation, anhedonia, cognitive impairment, and dysphoric mood (refer to Table 34.1).

Diagnosing MDD in breast cancer patients also is challenging because MDD diagnostic criteria include somatic symptoms often attributed to breast cancer or its treatment. For example, in a study of cancer patients with MDD, appetite changes and decreased concentration were associated with anhedonia. Sleep disturbance and fatigue were not significantly associated with nonsomatic symptoms, and these associations were consistent after adjusting for physical functioning and pain. Somewhat divergent from the results of Raison and Miller (2003), findings collectively suggested that appetite-related symptoms and diminished concentration may be particularly useful for diagnosing MDD in cancer patients, whereas sleep disturbances and fatigue may not be as useful (Akechi et al., 2003). Interesting strategies have been proposed for addressing symptom overlap in cancer patients (see Raison & Miller,

Table 34.1 Symptoms Common to Depression and Cancer-Related Cytokine Sickness

Anhedonia
Social Isolation
Fatigue
Weight Loss
Sleep Disturbance
Concentration and Memory Problems
Decreased Libido
Psychomotor Retardation
Depressed Mood[a]
Guilt and Worthlessness[a]
Suicidal Ideation[a]

[a]More common in depression.
Note. Table 34.1 was reprinted with permission (see Hopko, Colman, & Carvalho, 2008).

2003), including a two-system diagnostic approach based on inclusion and exclusion criterion largely dictated by whether the purpose of diagnosis is for research or clinical endeavors (Cohen-Cole, Brown, & McDaniel, 1993). Further complicating recognition and diagnosis of MDD may be a lack of patient symptom awareness, fear of stigma associated with mental illness, time constraints of the medical-care system (e.g., brief outpatient visits), and physician or oncologist unawareness regarding diagnostic symptoms of MDD. In any event, major depression, minor depression, or an adjustment disorder (and possibly co-existent anxiety disorders) are important considerations for breast cancer patients. There is no universally agreed upon system for diagnosing MDD in breast cancer patients, and for the most part, detection is most likely to occur in the context of patient self-report as provided during clinical interviews with physicians and oncologists. In some countries such as the United Kingdom, there are guidelines that dictate that screening for MDD in breast cancer patients should occur in primary care settings (NICE, 2004). Indeed, it is well documented that a significant number of patients with MDD present to medical-care settings (Kamphuisa et al., 2012). Problematically, although evidence based clinical guidelines are available, competent identification of MDD has proven difficult, and when identified, initiation and adherence to treatment is usually poor, and quality of care for depression in medical care settings generally is depicted as moderate to low (Rollman, Weinreb et al. 2006). This obstacle stated, there are a number of assessment strategies that may be useful toward accurately detecting depression in breast cancer patients. These methods are briefly reviewed here, with their appropriateness and clinical utility varying greatly across patient, assessment context, and level of professional training.

Unstructured and structured interviews. The structure of clinical interviews has tremendous variability, ranging from unstructured and completely flexible approaches to structured methods that are more restrictive and goal-directed. A number of positive correlates may be associated with unstructured methods that include increased therapist-patient rapport, ability to assess how patients organize responses, and the potential to explore unique details of a patient's history. Indeed, it is these brief unstructured interviews that are most commonly adopted by physicians and oncologists who may be assessing depression in breast cancer patients. Acknowledging pragmatic restrictions associated with using structured (clinician-rated) interviews in medical settings, there are a number of useful interviews that may be suitable for assessing depression in breast cancer patients. These interviews include the *Structured Clinical Interview for DSM-IV-Patient Version* (SCID-I/P; First et al., 1996), *Anxiety Disorders Interview Schedule* (ADIS-IV; Brown, Di Nardo, & Barlow, 1994), and the *Hamilton Rating Scale for Depression* (HRSD; Hamilton, 1960). These interviews all take approximately 60–90 minutes to administer as well as considerable training, and, therefore, may not be overly practical outside research settings. Because they generally have excellent psychometric properties, however, the expenses of requisite training and increased assessment time may be worth the effort if the primary objective is diagnostic certainty. In a fairly recent study utilizing a structured interview among women with Stage IV breast cancer, 33% of women were identified as satisfying *DSM-IV* criteria for MDD (Love et al., 2004).

Self-report measures

Self-report measures also may be useful for screening depression in breast cancer patients, as tools for monitoring progress during treatment, and as outcome measures for assessing the efficacy and effectiveness of various psychosocial and pharmacological interventions. Scales have been designed to assess a tremendous range of content areas, including

affective, verbal-cognitive, somatic, behavioral, and social symptoms of depression. At present, there are over 100 measures designed to assess depression and related constructs. The majority of these instruments have adequate to excellent psychometric properties (see Nezu et al., 2000). A few of the most commonly utilized measures are the Beck Depression Inventory (BDI-II; Beck, Steer, & Brown, 1996), Center for Epidemiological Studies for Depression Scale (CES-D; Radloff, 1977), and the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983). It is noteworthy that such depression measures are documented as having strong psychometric characteristics (i.e., reliability, validity, sensitivity, specificity, stable factor structures) across a number of divergent study samples, although, in general, they are highly understudied in breast cancer patients. To date, the most convincing support has been obtained for the HADS (Love et al., 2004; Payne et al., 1999) as well as the BDI-II and CES-D (Hopko et al., 2008). Important to highlight, even though self-report measures of depression may be useful in screening depression in breast cancer patients, there are some data that indicate interpretive modifications may be necessary (Love, Kissane, Bloch, & Clarke, 2002). Specifically, traditional cut-off scores for the HADS may result in underreporting of psychiatric morbidity in women with early stage breast cancer (Love et al., 2002). Finally, even though self-report measures have functional utility in screening depression in breast cancer patients, it has been established that use of such instruments in medical settings without a systematic approach to administering empirically validated psychosocial interventions ultimately results in limited symptomatic improvement (Coyne, Thompson, Palmer, Kagee, & Maunsell, 2000).

Observational methods

Breast cancer patients, family and friends, and treatment teams may increase the likelihood of detecting clinical depression through careful behavioral observation that extends beyond what might be detected via patient self-report or observed in the absence of patient acknowledgement of depression. In particular, observational methods involve an awareness of the frequency and duration of observable depressive behaviors that might include behavioral *excesses* such as crying; irritable/agitated behaviors; and even suicidal behaviors; or *deficits* such as minimal eye contact; psychomotor retardation; decreased recreational and occupational activities; as well as disruption in sleep, eating, and sexual behaviors. Related to the MDD criterion of anhedonia, behavioral avoidance is a pathognomonic feature of both mood and anxiety disorders, and a diagnosis of breast cancer may dramatically alter overt behavioral repertoires and subsequently limit exposure to rewarding environmental contingencies and thereby increase the likelihood of a mood and/or anxiety disorder. Indeed, some degree of behavioral avoidance or withdrawal is likely normative as a breast cancer patient ponders the diagnosis, potentially engages in ruminative behavior pertaining to rational or irrationally derived perceptions of the diagnosis, and particularly when the patient is undergoing highly enervating breast cancer treatment. Accordingly, when trying to distinguish between a more normative alteration in overt behavior versus an avoidance pattern that might be more suggestive of a mood disorder, contextual factors should be taken into account, such as time since diagnosis, cancer treatment status, degree of social support, and frequency and breadth of behavioral avoidance (i.e., localized or global avoidance of activities, hobbies, and social interactions). Important to consider when assessing or interpreting overt behavioral change, for some women the diagnosis and treatment of breast cancer is experienced as a traumatic stressor (Cordova, Studts, Hann, Jacobsen, & Andrykowski, 2000). On perhaps a more subtle level, breast cancer patients who are depressed also may interact differently in social situations. For example, behavioral research comparing depressed and nondepressed individuals suggests that the former group may exhibit a slower and more monotonous rate of speech, take longer to respond to the verbal behavior of others, smile less frequently, make less eye contact during conversation, hold their heads in a downward position more frequently, exhibit an increased frequency of self-focused negative remarks, and use fewer "achievement" and "power" words in their speech (Hopko, Lejuez, Armento, & Bare, 2004; Libet & Lewinsohn, 1973). Considering the strong and bidirectional link between decreased social skill and MDD (Segrin, 2000), it also is highly feasible that depressed breast cancer patients might be perceived as less competent in social situations, though this supposition has not been examined empirically. Knowledge of these correlates may contribute to recognition of depression in breast cancer patients, as might information obtained through behavioral monitoring diaries, where depressed and nondepressed individuals vary significantly with regard to how they spend their time and the amount of reward

they experience (Hopko, Armento, Chambers, Cantu, & Lejuez, 2003).

Psychosocial Treatments for Depressed Breast Cancer Patients

Primarily within the past two decades, a number of clinical trials have examined the efficacy of psychosocial and pharmacological treatments for breast cancer patients with depressive symptoms. Important to emphasize, the overwhelming majority of these studies have included breast cancer patients with subsyndromal depressive symptoms and have generally not included patients with systematically diagnosed depression (Fann et al., 2008; Hopko, Colman, & Carvalho, 2008; Newell et al., 2002; Sheard & Maguire, 1999; Williams & Dale 2006). As such, the extent to which positive effects of interventions extend beyond nonclinical samples toward clinically depressed patients is unclear, the latter population being more difficult to treat (Cuijpers et al., 2010; Williams et al., 2000). Pharmacological interventions for depression in breast cancer patients largely have focused on the efficacy of antidepressants, but also have involved treatment with psychostimulants, benzodiazepines, mood stabilizers, antipsychotics, and pain medications (Kissane et al., 2011; Rodin et al., 2007). In terms of antidepressant efficacy for depressed breast cancer patients, only a handful of studies have involved an exclusively breast cancer sample with well-diagnosed major depression. In general, these studies demonstrated the efficacy of both selective serotonin reuptake inhibitors (e.g., Paroxetine) and tricyclic antidepressants (e.g., Amitriptyline, Desipramine) in reducing depressive symptoms (Grassi, Biancosino, Marmai, & Righi, 2004; Moslinger-Gehmayr, Zaninelli et al., 2000; Musselman et al., 2006; Pezzella, Moslinger-Gehmayr, & Contu, 2001; Van Heeringen & Zivkov, 1996). In addition to these studies, other investigations including mixed-cancer samples or breast cancer patients with subclinical depression have demonstrated the effectiveness of various antidepressants in reducing depression and improving quality of life (cf. Fann et al., 2008). There are a few studies that were not supportive of antidepressant treatment (Razavi et al., 1996) or highlighted dangers associated with antidepressant use in breast cancer patients. In a very recent study, for example, Paroxetine use during tamoxifen treatment was associated with an increased risk of death from breast cancer, supporting the hypothesis that Paroxetine can reduce or abolish the benefit of tamoxifen in women with breast cancer (Kelly et al., 2010). It is certainly the case that pharmacotherapy for depression is a commonly used strategy in medical settings and is a viable treatment option for depressed breast cancer patients (American Psychiatric Association, 2000; Kissane et al., 2011). However, in the context of antidepressants not representing a panacea for depressed breast cancer patients, alternative treatment strategies are necessary because medication is often not recommended for patients with lower depression severity (Fournier et al, 2010), sometimes associated with dangers or unwanted side effects, and not always preferred by patients (Hollon & Shelton, 2001; van Geffen et al. 2009). In fact, there is a growing consensus that psychosocial treatment should be integrated into the routine care of patients with breast cancer (Jacobsen & Wagner, 2012). This position is based on an accumulating body of evidence on the deleterious effects of not addressing psychosocial needs, the beneficial effects of providing psychosocial services to address these needs, and data suggesting a sizeable portion of breast cancer patients do not receive needed psychosocial services (Jacobsen & Wagner, 2012).

Several empirically validated psychotherapies for depression (Chambless & Hollon, 1998; Hollon & Ponniah, 2010; Westen & Morrison, 2001) represent treatment options in medical-care settings (Cuijpers et al., 2009; Nieuwsma, 2011; Wolf & Hopko, 2008) and generally result in comparable outcomes to antidepressants (Bortolotti et al., 2008). In particular, it is evident that cognitive-behavioral and problem-solving therapies are associated with moderate effect sizes and show much promise in reducing depression in the context of medical-care settings (Hopko et al., 2011; Nezu et al., 2003; Nieuwsma, 2011; Wolf & Hopko, 2008). Prior to discussing the efficacy of psychosocial treatments for depressed breast cancer patients, a brief description of the most commonly utilized approaches is presented. Psychosocial treatments have been conducted in individual, group, couples, and family formats, and generally have included cognitive-behavioral strategies and psychoeducation, interpersonal psychotherapy, mindfulness-based therapy, supportive and/or expressive psychotherapy, cognitive-existential therapy, biofeedback, and hypnosis. *Cognitive-behavioral therapy* is strongly rooted in cognitive and behavioral research and refers to the process of modifying dysfunctional cognitions, overt behaviors, and emotional problems using various methods that often are provided in a manualized format and more

recently via computer administration. Such interventions are highly focused and time limited, and include cognitive restructuring, in which automatic and dysfunctional cognitions are identified, their rationality challenged, and more adaptive cognitions formulated (Beck et al., 1979). Behavior activation emphasizes structured attempts to increase overt behaviors that are likely to increase reinforcing environmental contingencies and corresponding improvements in thoughts, mood, and quality of life (Hopko, Lejuez, Ruggiero, & Eifert, 2003). Behavioral activation therapy is time limited and less complicated than many other depression interventions and engenders healthy nondepressed behavior by way of guided behavioral scheduling and avoidance reduction strategies. In a recent randomized clinical trial, our research group tested the efficacy of behavioral activation treatment for depression (BATD) compared to problem-solving therapy (PST) among breast cancer patients with major depression. Across both treatments, results revealed strong treatment integrity, excellent patient satisfaction with treatment protocols, and low patient attrition (19%). Moreover, intent-to-treat analyses suggested both treatments were efficacious, with both evidencing significant pre- and post-treatment gains across a breadth of outcome measures assessing depression, environmental reward, anxiety, quality of life, social support, and medical outcomes. These gains were associated with strong effect sizes, and based on response and remission criteria, approximately two-thirds of patients exhibited clinically significant improvement. Treatment gains were maintained at 12-month follow-up, with some support for stronger maintenance of gains in the BATD group. In addition to BATD and PST, other cognitive-behavioral interventions for depression include self-monitoring, communication, assertiveness, and social skills training, relaxation training, sleep hygiene and stimulus-control procedures, exposure-based treatments, and environmental contingency management. *Psychoeducation* often is provided as a component of cognitive-behavioral therapies and sometimes as a control condition in clinical trials. Psychoeducation involves the provision of information, feedback, and coping-skill options that are specific to the condition(s) being treated, and most often occurs very shortly following diagnosis or initiation of psychotherapy. For example, in behavioral activation for cancer patients, psychoeducation involves learning about the diagnosis of cancer, cancer statistics, cancer-related risk factors, emotional responses associated with being diagnosed with cancer, social-support resources, quality of life issues, and strategies for reducing depressive symptoms associated with the cancer diagnosis and treatment (Hopko & Lejuez, 2007).

Interpersonal psychotherapy (IPT)

Weissman & Markowitz, 1998) focuses on the interpersonal context, building interpersonal skills, and is based on the belief that interpersonal factors contribute greatly to psychological problems like depression. Interpersonal psychotherapy aims to modify interpersonal behavior by targeting interpersonal conflict, delayed grief reactions, role transitions and disputes, and social-skill deficits. *Mindfulness-based therapies* (MBT) are based on eastern spiritual philosophies (i.e., Buddhism) and facilitate intentional nonjudgmental awareness of present moment experiences. Mindfulness-based therapies include mindfulness-based stress reduction (MBSR) (Kabat-Zinn, 1990) and mindfulness-based cognitive therapy (MBCT) (Segal, Williams, & Teasdale, 2002). These group interventions involve teaching patients to cope with experiences in the present moment, including nonjudgmental awareness of feelings, thoughts and body sensations. MBT was designed to decrease experiential avoidance and increase emotional tolerance through accepting bodily sensations and emotional discomfort through mindfulness practices, including body scans, yoga, and walking and sitting meditations. Through increased mindfulness, patients learn attentional skills that allow them to recognize dysfunctional thought processes such as depression-related rumination, and to disengage from thoughts by redirecting attention to current experiences as they occur on a moment-to-moment basis (Kabat-Zinn, 1990; Segal et al., 2002).

Although different variants of supportive psychotherapy have been utilized with depressed breast cancer patients, the one most rigorously studied has been *supportive-expressive group therapy* (SEGT). Supportive-expressive group therapy typically involves weekly 90-minute group therapy sessions that may continue for over a year if indicated. The supportive-expressive therapy model involves the creation of a supportive environment in which patients are encouraged to confront problems, strengthen relationships, and discover enhanced meaning in their lives. Clinicians are trained to facilitate discussion of particular themes, with emphasis placed on exploring content in an emotionally expressive manner. The themes include: (a) building new bonds of social support, (b) facilitating emotional expression,

(c) confronting fears of death and dying, including coping with death of group members, (d) reordering life priorities, (e) improving communication and support with family and friends, (f) enhancing communication with physicians, and (g) learning to use self-hypnosis for anxiety and pain control (Classen, Butler, Koopman et al., 2001; Spiegel & Classen, 2000). Among breast cancer patients, particularly those with more advanced cancer, in addition to possible experiences of depression and anxiety, a number of existential issues may become more salient, including themes of spirituality, life values and purpose, and death and dying. To directly address such issues, cognitive-existential group therapy (CEGT: Kissane, Bloch, Miach et al., 1997) may be beneficial for resolving grief associated with loss, restructuring maladaptive cognitions, examining current and future life values and priorities, and improving problem-solving skills. The main objectives of CEGT are to address: (a) the cancer journey, (b) associated existential challenges, (c) the process of cancer treatment, (d) compliance with medical regimens, (e) cognitive re-appraisal of fears associated with cancer re-occurrence and unpredictability in life, (f) optimizing social support from family, friends, and a multidisciplinary treatment team, and (g) creating a more fulfilling life based on identification and engagement of behaviors associated with life values (Kissane et al., 2011). Highly related to both SEGT and CEGT is a relatively novel and unexamined form of individualized therapy referred to as CALM (managing Cancer and Living Meaningfully: Rodin, Lo, & Mikulincer, 2009). CALM involves an integrated theoretical approach and was designed for patients with advanced-stage illness. Therapy generally is administered intermittently (4–6 sessions) over a period of three months, with follow-up sessions scheduled when indicated. Incorporating social, behavioral, cognitive, and existential elements, treatment involves coverage of four patient modules: (a) symptom management and communication with health-care providers, (b) changes in self and interpersonal relationships, (c) spirituality and a sense of meaning and purpose, and (d) perceptions of the future, hope, and mortality. Finally, given that breast cancer is a disease that often impacts family and friends of the patient, it is important to acknowledge that, although the research base is limited, there are some data to support couple and family-based psychosocial interventions in the treatment of depressed breast cancer patients (Kissane, Mckenzie, Bloch et al. 2006; Manne et al., 2005).

Taken together, mental-health practitioners have a number of treatment alternatives that may be offered to depressed breast cancer patients, and ideally in close collaboration with physicians, oncologists, nurses, and other professionals involved with the patient. In terms of identifying the most optimal psychotherapeutic intervention, several factors should be considered, including prior experiences with psychotherapy, patient preferences, time restrictions associated with engagement in other responsibilities and demands that might include ongoing (and physically exhausting) cancer treatment, available social support resources, spiritual belief system, and stage of cancer illness and mortality risk (Kissane et al., 2011). Finally, and the focus of the next section, decisions should be made with reference to empirical studies examining the efficacy of psychosocial interventions for depressed breast cancer patients.

Psychosocial Treatment Efficacy

A number of qualitative and quantitative meta-analyses have examined the efficacy of psychotherapy in treating depression in cancer patients (Barsevick, Sweeney, Haney, & Chung, 2002; Boutin, 2007; Fann et al., 2008; Lepore & Coyne, 2006; Naaman, Radwan, Fergusson, & Johnson, 2009; Newell, Sanson-Fisher, & Savolainen, 2002; Sheard & Maguire, 1999; Tatrow & Montgomery, 2006; Williams & Dale, 2006). Among the psychosocial interventions evaluated in these reviews are predominantly those discussed in the previous section. These comprehensive reviews have been conducted with reference to general cancer samples as well as more specifically to breast cancer patients. In one of the earlier studies pertaining to the former, Trijsburg et al. (1992) reported psychological interventions generally were effective in managing both psychological symptoms as well as somatic symptoms such as pain. Sheard and Maguire (1999) examined 20 clinical trials (total n = 1,101) and noted a combined effect size of 0.36 standard deviations in favor of psychosocial treatment relative to no-treatment control groups. Group therapy and individual therapy were indicated as relatively comparable in treatment efficacy. In contrast to favorable support for psychotherapy for those with psychological distress, findings suggested that preventative psychological interventions for cancer patients might have limited clinical effects on preventing the manifestation of depression symptoms. Barsevick and colleagues (2002) examined two meta-analyses and nine randomized clinical trials with large

samples (n > 100) and reported that approximately 60–70% of studies examining behavior therapy, supportive counseling, or one of these interventions combined with cancer education resulted in significant attenuation of depressive symptoms in cancer patients. In a much less favorable report that included 329 published psychosocial intervention trials, Newell et al. (2002) reported that the methodological quality of randomized, controlled trials for depressed cancer patients was generally suboptimal, and that only very tentative recommendations could be stated about the effectiveness of psychological therapies for improving cancer patients' outcomes. Resulting in a very similar interpretation yet somewhat stronger criticism of the extant literature, Lepore and Coyne (2006) reported that, although higher-quality treatment outcome studies and more- sophisticated reviews were beginning to accumulate, the general literature (particularly the more rigorous reviews) did not make a compelling case for the efficacy of psychosocial interventions for cancer patients. Also consistent with this review, Williams and Dale (2006) indicated that, in the context of highly significant methodological limitations, there was very limited evidence to support the efficacy of psychosocial interventions for depressed cancer patients, which incidentally, also applied to the pharmacological treatment of cancer patients with antidepressants. Among the many significant limitations highlighted in this review was the accurate appraisal that the overwhelming majority of clinical psychotherapy trials had failed to distinguish between cancer patients with subsyndromal depressive symptoms and those with diagnosable major depression. This sentiment was also addressed in the most recent of reviews, in which it was concluded that, although randomized controlled trials (of moderate quality) suggested some support for psychotherapy in treating depressive symptoms in advanced cancer patients, no evidence supported the efficacy of these treatments for patients with well-diagnosed major depression (Akechi et al., 2008).

Several reviews also have been conducted with exclusively breast cancer patient samples. In a meta-analysis on the effects of cognitive-behavioral therapies in reducing distress and pain in breast cancer patients, although several methodological limitations of reviewed studies were noted, Tatrow and Montgomery (2006) reported moderate effect sizes for psychological distress (d = 0.31) and pain (d = 0.49), and indicated roughly two-thirds of breast cancer patients who received CBT had less distress and pain relative to control groups. Individualized psychotherapy for distress also had significantly larger effects compared to group psychotherapy, and there were no significant differences in outcomes as a function of whether metastasis was present. In a review of 20 studies of cognitive behavioral therapy, supportive-expressive group therapy, and their combination, Boutin (2007) determined that all three treatments reduced negative affect in women with breast cancer, although the incremental benefits of combining treatments were unclear. Similar to concerns forwarded in the more general cancer psychotherapy reviews (Lepre & Coyne, 2006; Williams & Dale, 2006), it also has been documented that treatment outcome studies of depressed breast cancer patients have largely included samples with general distress and mixed-depressive states, with minimal systematic work with breast cancer patients with well-diagnosed depression (Fann et al., 2008). Finally, in the most recent review of psychosocial treatments for depressed breast cancer patients (Naaman et al., 2009), clinically moderate-to-strong effect sizes were found in trials assessing treatments for depression (d = 1.01) mixed depressive-anxiety clinical presentations (d = 0.47) and quality of life (d = 0.74). These authors also suggested that more abbreviated treatments focusing on coping skills may be more suitable for early-stage breast cancer patients, whereas those with advanced breast cancer may benefit more from longer-term interventions emphasizing support and deeper emotional processing (Naaman et al., 2009).

Given that the most recent reviews of psychosocial interventions for depression in breast cancer patients was several years ago and the fact that many treatment outcome studies were not included in these reviews or had not yet been conducted, our research team synthesized the current literature and reported findings in Table 34.2. To be included in the review, studies (a) must have exclusively included a sample of breast cancer patients (i.e., no mixed cancer samples), (b) must have included at least one depression index as a primary outcome measure, and (c) must have presented enough detail about the psychosocial intervention utilized to allow for adequate description. To be included, studies did not have to be randomized controlled trials and did not have to include breast cancer patients with well-diagnosed depression or present follow-up data to assess maintenance of gains. Following comprehensive literature searches on both PsycINFO and Medline/Pubmed, a total of 57 eligible studies were identified: Mindfulness-based therapy (8),

Table 34.2 Psycho-Social Interventions for Depressed Breast Cancer Patients

Study	Sample	Interventions and Research Design	Duration	Primary Results
Mindfulness-Based Therapy				
Dobkin (2008)	• N = 13 • Age (*M* = 54 years) • Moderate depression • Stage: Not reported • Time since diagnosis: within past two years	Group: 1. MBSR Design: OT	• 8 weekly sessions (2.5 hours each)	• At post-treatment, self-reported depression decreased and mindfulness increased • Decrease in depressive symptoms did not reach statistical significance
Henderson et al. (2011)	• N = 163 • Age = 20–65 • Mild depression • Stage: I or II • Time since diagnosis: within past 2 years	Group: 1. MBSR 2. Nutrition education (NE) 3. Supportive counseling Design: RT	• MBSR and NE: 7 weekly sessions (2.5 hours each) and 1 session (7.5 hours) • SC: 3 monthly sessions (2 hours each)	• Significant improvements in quality of life, depression, anxiety, emotional control, and coping outcomes for the MBSR compared to NE and SC • Effect declined at 24-month FU
Hoffman et al. (2012)	• N = 214 • Age (*M* = 49 years) • Stage: 0, II, or III • Time since diagnosis: 18 months	Group: 1. MBSR 2. WL Design: RCT	Group: • MBSR: 8 weekly sessions and 1 session (6 hours)	• Significant reductions in anxiety and depression for MBSR group compared to WL
Lengacher et al. (2009)	• N = 82 • Age (*M* = 58 years) • Mild depression • Stage: 0, II, or III • Time since diagnosis: 18 months	Group: 1. MBSR 2. Usual care (UC) Design: RCT	• MBSR: 6 weekly sessions (2 hours each) • UC on waitlist for MBSR	• Significantly lower depression, anxiety, and fear of cancer recurrence, and improved physical functioning in MBSR group

Lengacher et al. (2011)	• N = 17 • Age (*M* = 57 years) • Mild depression • Stage: 0, II, or III • Time since diagnosis: end of cancer treatment to 1 year post-treatment	Group: 1. MBSR Design: OT	• 8 weekly sessions (2 hours each)	• Significantly lower depression, state and trait anxiety, perceived stress, fear of cancer recurrence and improved quality of life at post-treatment
Matousek, & Dobkin (2010)	• N = 57 • Age (*M* = 56 years) • Mild to moderate depression • Stage: 0 or II (n=39), III (n=2), IV (n = 6), unknown (n = 10) • Time since diagnosis: 2–340 months post cancer treatment	Group: 1. MBSR Design: OT	• 8 weekly sessions (2.5 hours each) and 1 day session (6 hours)	• Significant reductions in stress and depression; improved medical symptoms; improved mindfulness and emotional coping
Shapiro et al. (2003)	• N = 63 • Age (*M* = 57 years) • Moderate depression • Stage: II • Time since diagnosis: 2–25 months post cancer treatment	Group: 1. MBSR 1. Free choice (FC) Design: RT	• MBSR: 6 weekly sessions (2 hours each) and 1 session (6 hours) • FC: various stress management activities to choose from	• Participants in the MBSR who reported greater mindfulness practice had improved sleep quality • Specific depression and anxiety outcomes not reported
Würtzen et al. (2013)	• N = 267 • Age: (*M* = 54 years) • Stage: I, II, or III • Time since diagnosis: 8 months	Group: 1. MBSR 2. Treatment as usual (TAU) Design: RCT	• MBSR: 8 weekly sessions and 1 day session (5 hours)	• Reductions in depression and anxiety for MBSR group compared to TAU

(continued)

Table 34.2 Continued

Study	Sample	Interventions and Research Design	Duration	Primary Results
Problem-Solving Therapy				
Akechi et al. (2008)	• N = 4 (Japanese) • Age (*M* = 45 years) • Depression: minimal to severe • Stage: early (75%) and locally advanced (25%) • Time since diagnosis: Range from 13–53 months	Individual: 1. Problem-solving therapy Design: OT	• 6 sessions (10–20 weeks) • One participant completed 3 sessions (4 weeks)	• Depression and anxiety scores decreased following PST • Treatment gains not maintained at 6- or 12-month follow-up
Allen et al. (2002)	• N = 164 • Age (*M* = 42 years) • Moderate depression • Stage: I, II, III, IV • Time since diagnosis: Not reported	Individual: 1. PST (home-based care) 2. Minimal contact (MC) Design: RT	• PST: 2 in-person sessions (2 hours each) and 4 telephone calls (2 weeks apart) • MC: 1 session of problem-solving skills	• Significantly lower unmet needs and better overall mental health at 1-month follow-up for PST group • At 5-month follow-up, mental health improvements were not maintained
Carvalho & Hopko (2009)	• N = 1 • Age: 29 years • Moderate depression • Stage: III • Time since diagnosis: 6 months	Individual: 1. Problem-solving therapy Design: CS	• 8 weeks, 1 hour weekly	• Decreased depression, anxiety, and increased quality of life and medical outcomes at post-treatment
Hosaka, Sugiyama, Tokuda, & Okuyama (2000)	• N = 47 Japanese women • Age: ((*M* = 51 years) • Mild to moderate depression • Stage: Not reported • Time since diagnosis: Not reported	Group: 1. Problem-solving, psycho-education, psychological support, relaxation training, and guided imagery Design = OT	• 5 sessions (90-minutes)	• Decreased depression, anxiety, and total mood disturbances at post-treatment and 6-month follow-up among patients who had no psychiatric diagnoses at pretreatment

Supportive Psychotherapy				
Björneklett, et al. (2012)	• N = 382 • Age ((*M* = 58 years) • Mild to moderate depression • Stage: Not reported. Time since diagnosis: Within first year following diagnosis	Group: 1. Support group (SG) 2. Control group (CG) Design: RCT	SG: 7 day residential support therapy program CG: Standard follow-up medical appointments	Decreased anxiety at 2, 6, and 12 months following treatment in SG group Levels of depression unchanged by SG
Burton et al. (1995)	• N = 295 • Age (*M* = 62 years) • Mild to moderate depression • Stage: I (8%), II (56%), III (35%), IV (1%) • Time since diagnosis: Not Reported	Individual: 1. Preoperative interview and stress reduction (PI-S) 2. Preoperative interview and chat (PI-C) 3. Preoperative interview: PI 4. Routine care Design: RCT	PI-S: 30 minutes psychotherapeutic intervention PI-C: 30 minute chat	PI-S, PI-C, and PI groups reported significantly less depression at 1-year follow-up PI-S superior to chat for patients with severe life stressors
Classen, et al. (2001)	• N = 102 • Age: (*M* = 54 years) • Mild to moderate depression • Stage: Metastatic breast cancer • Time from metastatic diagnosis to study entry: SEGT: M = 23 months; CG, M = 32 months	Group: 1. Supportive-expressive group therapy (SEGT) 2. No-treatment control (educational materials on breast cancer provided) Design: RCT	SEGT: weekly, 90-minutes sessions and women encouraged to participate for 1 year	Primary analysis: SEGT evidenced no significant reductions in depression but reductions in traumatic stress Secondary analysis: (final assessment data within 1 year of death removed), significant decline in mood disturbance (*d* = 0.25) for SEGT group.

(continued)

Table 34.2 Continued

Study	Sample	Interventions and Research Design	Duration	Primary Results
Classen et al. (2008)	• N = 357 • Age: (*M* = 50 years) • Mild to moderate depression • Stage: I through IIIA • Time since diagnosis: *M* = 9 months	Group: 1. Supportive-expressive group therapy (SEGT) 2. No-treatment control (educational materials on breast cancer provided) Design: RCT	SEGT: 12 weekly, 90-minutes sessions	No significant reductions in depression or anxiety at post-treatment or through 2-year follow up Reduced depression at post-treatment when patient outlier included in data analysis
Fukui et al. (2000)	N = 50 • Age: ((*M* = 53 years) • Mild to moderate depression • Patients with major depression diagnosis excluded • Stage: Primarily II (80%) • Time since diagnosis: Not reported	Group: 1. Supportive stress management (SSM) 2. Wait-list control Design: RCT	SSM: 1.5 hours, weekly, for 6 weeks (support, stress management, education, and coping)	Decreased depression and anxiety in the SSM group at post-treatment Improvements maintained at 6-months follow-up
Goodwin, et al., (2001)	• N = 235 • Age: ((*M* = 50 years) • Mild to moderate depression • Stage: I (24%), II (28%), III (9%), IV (7%), TX (32%). • Time since diagnosis: *M* = 5.2 months	Group: 1. Supportive-expressive group therapy (SEGT) 2. No-treatment control (educational materials on breast cancer provided) Design: RCT	SEGT: weekly, 90-minutes sessions and women encouraged to participate for 1 year	Significantly reduced depression in the SEGT group and results maintained at 1-year follow-up SEGT did not influence survival rates

Gotay et al. (2007)	• N = 305 • Age: Range = 25–93 years • Moderate depression • Stage: Not reported • Time since diagnosis: ≥ 2 years	Individual: 1. Telephone counseling (TC) 2. Usual Care Design: RCT	TC: 4–8 telephone calls over 1 month	No significant group differences in overall distress or depressive symptoms at 3 months follow-up
Kissane, et al. (2007)	• N = 163 • Age: ((*M* = 52 years) • Moderate depression as assessed via clinical interview • Stage: I, II, III, IV, and unknown all included • Time since diagnosis: *M* = 65 months	Group: 1. Supportive-expressive group therapy (SEGT) 2. Minimal treatment control group (MT) Design: RCT	SEGT: weekly, 90-minutes sessions and women encouraged to participate for 1 year (*M* = 37 sessions) MT: 3, 1-hour, relaxation classes over 3 weeks	Women with less severe depression at baseline fared better in SEGT, such that they had an increased likelihood of remaining nondepressed relative to patients in MT. At 6 months post-treatment, 18% *DSM-IV* diagnosis of depression in SEGT group and 40% in MT.
Maguire et al. (1980)	• N = 152 • Age: Not reported • Moderate depression assessed via clinical interview • Stage: Women admitted for mastectomy • Time since diagnosis: Not reported	Individual: 1. Counseling 2. Usual care Design: RCT	Counseling: specialist nurse provided support every 2 months at home for up to 1 year and number of sessions varied across patients	Counseling group reported fewer physical complaints, responded better psychologically to breast loss, and reported fewer difficulties with social and sexual relationships Episodes of depression and anxiety shorter for counseling group

(continued)

Table 34.2 Continued

Study	Sample	Interventions and Research Design	Duration	Primary Results
Marchioro et al. (1996)	• N = 36 • Age: Range = 35–65 years • Mild to moderate depression • Stage: Nonmetastatic • Time since diagnosis: Not reported	Individual: 3. Counseling 4. Usual care Design: RCT	Counseling: weekly 50 minute session of and bimonthly family counseling	Significantly reduced depression and improved quality of life in the Counseling group Results maintained through 9-month follow-up
McArdle et al., (1996)	N = 272 • Age: (Median = 55– 66 years) • Mild to moderate depression • Stage: Not reported • Time since diagnosis: Not reported	Group: 1. Treatment as usual (TAU) 2. Breast care nurse (BCN) 3. Tak Tent (TT: Voluntary organization) 4. BCN + TT Design: RCT	BCN: psychoeducation and support counseling TT: psychoeducation and support counseling from Tak Tent BCN + TT: combined BCN and TT	Depression decreased and general health improved across the 12-month assessment period for all groups Depression decreased most in patients treated with BCN
Montazeri, et al., (2001)	• N = 56 • Age: ((M = 45 years) • Mild to moderate depression • Stage: Not reported • Time since diagnosis: primarily diagnosed 1–5 years ago (84%).	Group: Individual: 1. Iranian breast cancer support group (IBCS). Design: OT	IBCS: 1 year duration	Significant reductions in depression and anxiety at post-treatment.
Spiegel, Bloom, & Yalom (1981)	• N = 58 • Age: ((M = 55 years) • Mild to moderate depression • Stage: Metastatic breast cancer • Time since diagnosis: Not reported	Group: 1. Cancer support group 2. No-treatment control group Design: RCT	Cancer support group: Weekly, 90-minutes sessions; assessment through 1 year	Significantly decreased mood disturbance in support group and fewer maladaptive coping strategies Reduced depression in the support group but not statistically significant

Spiegel, Morrow et al. (1999)	• N = 115 • Age: (*M* = 52 years) • Mild to moderate depression • Stage: I or II • Time since diagnosis: M = 8 months	Group: 1. Supportive-expressive group therapy (SEGT) Design: OT	SEGT: 12 weekly 90-minute sessions	Reduced depression at post-treatment that were maintained at 12-month follow-up
Watson, Denton, Baum, & Greer (1988)	• N = 40 • Age: Not reported • Moderate depression • Stage: Women treated with mastectomy • Time since diagnosis: Not reported	Individual: 1. Counseling 2. Usual care Design: RCT	Counseling: provided by a specialist nurse	Significantly reduced depression in counseling group at 3 months postoperation and increased perceptions of personal control over health At 12 months post operation, no significant group differences
Winzelberg, et al. (2003)	• N = 72 • Age: (*M* = 50 years) • Mild to moderate depression • Stage: Not reported • Time since diagnosis: M = 12 months	Group: 1. Bosom buddies (BB) 2. Wait-list control Design: RCT	BB: 12-week, structured, web-based support group	Significant reductions in depression at post-treatment for women in the BB group
Youssef (1984)	• N = 18 • Age: Range = 27–60 years • Moderate depression • Stage: Not Reported • Time since diagnosis: Not Reported	Group: 1. Crisis intervention (CI) 2. Usual care Design: RCT	CI: 18 sessions (1 hour, 3 times a week for 6 weeks) provided in the hospital and focused on mindful coping	Significant decrease in depression and improvement in self-esteem in CI group from pre- to posttreatment

(continued)

Table 34.2 Continued

Study	Sample	Interventions and Research Design	Duration	Primary Results
Psychoeducation				
Stanton et al. (2005)	• N = 551 • Age: (*M* = 58 years) • Mild to moderate depression • Stage: I and II • Time since diagnosis: Not reported	Group: 1. Psycho-educational counseling (EDU) 2. Peer-modeling videotape (VID) 3. Control (CTL) Design: RCT	EDU: 1 session (80-min), and 1 telephone session with cancer educator. Also received "moving beyond Cancer" video. VID: Received NCI publication, "Facing Forward" and a 23-min cancer education film. CTL: "Facing Forward	No significant effect of interventions on cancer-specific distress VID produced significant improvement in energy/fatigue at 6 months relative to CTL No significant group effects on primary outcomes at 12 months follow-up
Yates et al. (2005)	• N = 110 • Age: (*M* = 49 years) • Mild to moderate depression • Stage: I (14%) Stage II: (86%) • Time since diagnosis: Not reported	Group: 1. Psycho-educational counseling (EDU), based on PRECEDE 2. General education control group (GE) Design: RCT	EDU: 3 individualized, weekly sessions (10–20 minutes) and provided informational materials GE: Sessions equivalent in number and timing	No significant post-treatment differences for: depression, anxiety, confidence managing fatigue, cancer self-efficacy, or quality of life.
Biofeedback				
Gruber et al. (1993)	• N = 13 • Age (*M* = 45 years) • Mild to moderate depression • Stage: All patients stage I • Time since diagnosis: Not reported	1. Biofeedback (BF) 2. Wait-list control Design: RCT	BF: 9 weeks of group relaxation training, guided imagery, and BF (EMG, skin conductance, hand temperature), which occurred twice per week	Significant BF effects found in natural killer cell activity, lymphocyte responsiveness, and number of peripheral blood lymphocytes No significant reduction of depression or anxiety following treatment

Interpersonal Psychotherapy				
Badger, Segrin, Dorros, Meek & Lopez (2007)	• N = 96 (and partners) • Age (*M* = 54 years) • Mild depression • Stage: Stage I-III, currently in treatment for breast cancer • Time since diagnosis: Not Reported	Individual: 1. Telephone Interpersonal Counseling (TIP-C) 2. Self-managed low impact exercise (EX) 3. Attention control group (AC) Design: RCT	6-week telephone-therapy for patients and partners called semimonthly TIP-C: Telephone IPT and cancer education EX: Calls to encourage exercise AC: Printed information on cancer and brief calls	Depression decreased for patients and partners in each condition Patients in TIP-C and EX evidenced greater decreases in depression than the AC group
Badger et al. (2004)	• N = 1 and her partner • Age = 54 years • Diagnosed as depressed via clinical interview • Stage: II Time since diagnosis: 4 months	Individual: 1. Telephone Interpersonal counseling (TIP-C) Design: CS	6-week telephone-administered therapy and partner received calls semi-monthly	Depression outcome unclear
Badger et al. (2005)	• N = 24 • Age: (*M* = 53 years) • Mild to moderate depression • Stage: Primarily Stage II • Time since diagnosis: Not reported	Individual: 1. Telephone Interpersonal Counseling (TIP-C) Design: OT	6 -week telephone-administered therapy	Decreased depression and fatigue and improved quality of life at post-treatment
Donnelly et al. (2000)	• N = 14 (and partners) • Age: (*Median* = 45 years) • Depression severity unclear • Stage: IV • Time since diagnosis: Recruited following consent for chemotherapy	Individual: 1. Telephone IPT Design: OT	Weekly telephone IPT following initiation of chemotherapy and ending 4 weeks after treatment (mean number of sessions: 16: patients; 11: partners)	Depression outcome unclear

(continued)

Table 34.2 Continued

Study	Sample	Interventions and Research Design	Duration	Primary Results
Cognitive Behavioral Therapy				
Antoni et al., (2001)	• N = 100 • Age: (M = 50 years) • Mild to moderate depression • Stage: 0–II • Time since diagnosis: Less than one year	Group: 1. Cognitive-behavioral stress management (CBSM) 2. Control group (CG) Design: RT	CBSM: 10 weekly 2-hour sessions CG: Psycho-education and training in relaxation and cognitive therapy (1-day: 6 hours)	CBSM reduced prevalence of moderate depression and increased patient optimism Treatment gains maintained at 3-month follow-up
Antoni et al. (2009)	• N = 128 • Age: ((M = 50 years) • Mild to moderate depression • Stage: 0–3 breast cancer • Time since diagnosis: 4–8 weeks post-surgery	Group: 1. Cognitive-behavioral stress management (CBSM) 2. Control group (CG) Design: RT	CBSM: 10 weekly 2-hour sessions CG: Psycho-education, relaxation and cognitive restructuring (1-day: 6 hours)	CBSM reduced negative affect and cortisol levels at post-treatment Treatment gains maintained through 12-month follow-up
Armento & Hopko (2009)	• N = 1 • Age: 58 years • Moderate depression • Stage: II • Time since diagnosis: 2 years	Individual: 1. Behavioral Activation Design: CS	BA: 8 weeks, 1 hour weekly	Decreased depression, anxiety, and increased quality of life and medical outcomes at post-treatment Results maintained at 6-months follow-up
Beatty & Koczwara (2010)	• N = 5 • Age: range = 45–63 years • Mild to moderate depression • Stage: 0–II • Time since diagnosis: Not Reported	Group: 1. Cognitive-behavioral stress management (CBSM) Design: OT	CBSM: 10 weekly 2-hour sessions	Reduced depression at post-treatment (d = 0.54) Gains not sustained at one-month follow up (d = 0.13)

Boesen et al., (2011)	• N = 210 • Age: Range = 30–70 years • Mild tomoderate depression • Stage: I (24%), II (46%), III (20%), missing (10%) Time since diagnosis: Not reported	Group: 1. Cognitive-existential group therapy (CEGT): 2. Control group (CG) Design: RCT	CEGT: 2 weekly, 6-hour sessions of psycho-education and 8 weekly 2.5-hour sessions of group psychotherapy	No significant effects of CEGT on psychological distress, quality of life, or marital satisfaction
Bridge, Benson, Pietroni, & Priest (1988)	• N = 139 • Age: (*M* = 53 years) • Mild to moderate depression • Stage: I or II • Time since diagnosis: Not Reported	Individual: 1. Muscle relaxation (MR) 2. Muscle relaxation and peaceful imagery (MRPI) 3. Verbal expression control group (CG) Design: RCT	6 weekly sessions	Reduced depression and anxiety in MR and MRPI groups No differences between MR and MRPI
Christensen (1983)	• N = 20 couples • Age: (*M* = 40 years) • Mild-Moderate depression • Stage: Not reported • Time since diagnosis: mastectomy 2–3 months ago	Couples counseling: 1. Cognitive-behavioral therapy (CBT) 2. Control group Design: RCT	CBT: social skills and problem-solving skills, psychoeducation, stress management	CBT reduced emotional discomfort in both partners, reduced depression in the patient, and increased sexual satisfaction for both spouses
Edelman, Bell, & Kidman (1999a)	• N = 124 patients • Age: Range = 29–65 years • Mild to moderate depression • Stage: Metastatic breast cancer • Time since diagnosis: Not reported	Group: 1. Cognitive-behavioral therapy (CBT) 2. No-treatment control Design: RCT	CBT: 8 weeks of group CBT followed by a family night and 3 further monthly sessions	CBT group had reduced depression and increased self-esteem at post-treatment Gains not sustained at 3- and 6- month follow-up

(continued)

Table 34.2 Continued

Study	Sample	Interventions and Research Design	Duration	Primary Results
Edelman, Bell, & Kidman (1999b)	• N = 60 • Mild to moderate depression • Stage: all stages • Time since diagnosis: newly diagnosed breast cancer	Group: 1. Cognitive-behavioral therapy (CBT) 2. Supportive counseling Design: RT	12 weekly sessions	Reduced depression and improved quality of life and self-esteem in both groups at post-treatment with CBT group more improved. No differences at 4-month follow up
Edmonds et al. (1999)	• N = 66 • Age: (*M* = 51 years) • Mild to moderate depression • Stage: Metastatic breast cancer • Time since diagnosis: Not Reported	Group: 1. Cognitive-behavioral therapy (CBT) 2. Educational control group (EC) Design: RCT	CBT: 32 weeks of CBT and "intensive weekend skills training" (14 hours) EC: Provided educational materials	Minimal difference between CBT and EC at post-treatment as well as 4, 8, and 14 month follow-ups on measures of distress and mood
Hopko et al. (2011)	• N = 80 • Age: (*M* = 55 years) • Patients diagnosed with major depression using structured interview • Stage: 0 (26%), I (28%), II (32%), III (11%), IV (3%) • Time since diagnosis: 3.2 years	Individual: 1. Brief behavior activation (BA) 2. Problem-solving therapy (PST) Design: RT	8 (1-hour sessions)	Both interventions equally effective in decreasing depression and anxiety and improving medical outcomes and quality of life All treatment gains maintained through 12-month follow-up

Kissane et al (2003)	• N = 303 • Age: (*M* = 46 years) • Patients structured interview (10% major depression; 27% minor depression • Stage: I (17%), II (83%) • Time since diagnosis *M* = 3 months post-surgery	Group: 1. Cognitive-existential group therapy (CEGT) 2. Relaxation control (RC) Design: RT	CEGT: 20 weekly 90-minute sessions and 3 relaxation classes RC: 3 relaxation classes	Trends for the CEGT group for depression, anxiety, and family functioning
Manne, Ostroff et al. (2005)	• N = 238 couples • Age: (*M* = 46 years) • Mild to moderate depression • Stage: 0-IIIA • Time since diagnosis: underwent surgery within past 6 months	Group: 1. Couples-based cognitive-behavioral therapy (CBT) with stress management, relaxation training, sensate focus, communication and problem-solving skills 2. Usual care (UC)	CBT: 6 weekly 90-minute sessions	Decreased depression and anxiety in the CBT group at post-treatment through 6-month follow-up
McKierna, Steggles, Guerin, & Carr (2010)	• N = 69 • Age: (*M* = 51 years) • Mild to moderate depression • Stage: I or II • Time since diagnosis: Not reported	Group: 1. Cognitive-behavioral therapy (CBT) 2. Psychoeducational control (PC) Design: RT	CBT: 6 weekly 90-minute sessions	No post-treatment differences on depression, coping, and quality of life CBT patients had post-treatment reduction in problem severity and impact of problems that was maintained at 6-month follow-up

(continued)

Table 34.2 Continued

Study	Sample	Interventions and Research Design	Duration	Primary Results
Perna et al. (2010)	• N = 51 • Age: (*M* = 51 years) • Generally obese • 44% African American • Mild to moderate depression • Stage: 0, I, II, or IIIa • Time since diagnosis: "recent" diagnosis	Group: 1. Structured exercise and self-monitoring (SESI) 2. Information control (IC) (physical assessment results and exercise brochure) Design: RT	SESI: Aerobic exercise 3 times per week (30 min) and light weights at hospital for 4 weeks, then same at home. Also two 30-min exercise counseling sessions IC: 45-minute information session	At 3 month follow up, there was significantly less depression in the SESI group relative to IC
Savard et al. (2005)	• N = 58 • Age: (*M*=54 years) • Mild to moderate depression • Stage I-III • Time since diagnosis: *M* = 42 months	Group: 1. Cognitive-behavioral therapy (CBT) 2. Wait-list control (WL) Design: RCT	CBT: Eight weekly sessions (90 minutes)	Significantly reduced depression in the CBT group at post treatment
Savard et al. (2006)	• N = 45 • Age: (*M* = 51 years) • Moderate depression • Stage: IV (metastatic) • Time since diagnosis: Not reported	Individual: 1. Cognitive therapy (CT) 2. Wait-list control (WL) Design: RCT	CT: 8 weekly sessions and 3 booster sessions (3-week intervals) following CT	CT: lower clinician-rated depression at post-treatment but no group differences in self-reported depression (i.e., reduced and equivalent through treatment and 6 month follow-up

Simpson, Carlson, & Trew (2001) and also see Simpson, Carlson et al. (2002)	• N = 89 • Age: (*M* = 50 years) • Mild to moderate depression • 26% depression diagnosis as per structured interview • Stage: 0, I, or II • Time since diagnosis: Up to 2 years post-cancer treatment	Group: 1. Cognitive-behavioral therapy (CBT) including progressive muscle relaxation, self-hypnosis, stress management, mental imagery, goal setting 2. Control group (CG): self-initiated workbook study Design: RCT	CBT: Six weekly 90-minute group sessions	Reduced depression in CBT group at post-treatment No group differences at 1-year follow-up but CBT group has reduced depression at 2-year follow-up
Hypnosis				
Elkins et al. (2008)	• N = 60 • Age: (*M* = 57 years) • Mild to moderate depression • Stage: Not reported • Time since diagnosis: Not reported	Individual: 1. Hypnosis 2. No treatment Design: RCT	Hypnosis: Five weekly sessions of 50 minutes	Reduced depression, anxiety, hot flashes, and improved sleep for patients in the hypnosis group
Schnur et al. 2009	• N = 40 • Age: Range = 30–80 years • Mild to moderate depression • Stage: 0, I, II, or III • Time since diagnosis: Not reported	Individual: 1. Cognitive-behavioral therapy and hypnosis (CBTH) 2. Usual care control (UC) Design: RCT	CBTH: Patients met with clinicians twice per week during radiotherapy and learned hypnosis and cognitive restructuring	CBTH reduced negative affect and increased positive affect during radiotherapy

(continued)

Table 34.2 Continued

Study	Sample	Interventions and Research Design	Duration	Primary Results
Spiegel & Bloom, (1983)	• N = 58 • Age: (*M* = 55 years) • Mild to moderate depression • Stage: IV (metastatic) • Time since diagnosis: (M = 25 months)	Group: 1. Supportive therapy and hypnosis for approximately 50% of patients (ST-H) 2. No-treatment control (CG) Design: RCT	ST-H: weekly 90 minute sessions lasting several years if needed	Attrition across 1-year (50% due to death) complicated data analyses Among survivors, depression, anxiety, and pain sensations were reduced

Research Design Abbreviations
RCT = Randomized Controlled Trial
RT = Randomized Trial
OT = Open Trial
CS = Case Study
Note. Table 34.2 was created by the authors for this chapter.

problem-solving therapy (4), supportive psychotherapy (17), psycho-education (2), biofeedback (1), interpersonal psychotherapy (4), cognitive-behavior therapy (18), and hypnosis (3).

To summarize findings, the following observations were made: (a) the overwhelming majority of published studies found psychosocial interventions effective in reducing symptoms of depression, anxiety, pain, and hostility in breast cancer patients, as well as increasing quality of life, coping skills, self-efficacy, and general optimism; (b) this finding is, logically, at least partially impacted by publication bias (in favor of studies reporting positive outcomes), and there are several published studies in which psychosocial interventions had minimal effects in reducing depression (e.g., Björneklett et al., 2012; Boesen et al., 2011; Classen et al., 2008; Edmonds et al., 1999; Gotay et al., 2007; Gruber et al., 1993; McKierna, Steggles, Guerin, & Carr, 2010; Stanton et al., 2005; Yates et al., 2005); (c) in the past decade, there has been increasing support for mindfulness-based therapy as an effective treatment for depressed breast cancer patients and further work in this area is highly encouraged; (d) in addition to mindfulness-based therapies, there are highly supportive data on the efficacy of structured counseling approaches (e.g., SEGT) and cognitive-behavioral therapies in effectively reducing depression symptoms; (e) given the efficacy of problem-solving therapy and interpersonal psychotherapy in treating individuals with major depression (Hollon & Ponniah, 2010; Wolf & Hopko, 2008) and our recent study documenting the efficacy of the former in treating breast cancer patients with well-diagnosed depression (Hopko et al., 2011), it is highly surprising how understudied these interventions are in breast cancer samples; (f) purely psycheducational and biofeedback interventions appear to have no support in treating depression in breast cancer patients and should not be considered viable treatment options; (g) significantly more work is required to establish the efficacy of hypnosis in treating depressed breast cancer patients; (h) a vast majority of treatment outcome studies continue to be characterized by significant methodological limitations (Lepore & Coyne, 2006; Williams & Dale, 2006), the most significant of which is that the overwhelming majority of studies are conducted on breast cancer patients without a diagnosis of major depression as ascertained via structured clinical interviewing procedures; (i) along with overextensive study of breast cancer patients with poorly defined depression severity, in many cases, samples are inadequately described with regard to cancer stage, time since cancer diagnosis, cancer treatment, and co-existent mental-health and medical conditions, ans as such, generalizability of data to patients with a wider scope of demographic, medical, psychiatric, and functional difficulties is questionable; (j) outcome measures in the literature are limited primarily to core clinical (depressive) symptoms, and only infrequently has attention been given to coexistent symptoms (anxiety), functional status (quality of life, medical outcomes, social support), and service utilization; (k) with very few exceptions, long-term follow-up of depressed breast cancer patients treated via psychosocial (and pharmacological) interventions generally have not been conducted; (l) at this stage of research, we understand very little about factors that predict treatment outcome among depressed breast cancer patients, and in a recent study integrating data on a heterogeneous sample of over 3,000 cancer patients, those with poorer quality of life, fewer interpersonal relationships, decreased sense of control, low levels of optimism and neuroticism, high levels of emotional expressiveness, and high interpersonal sensitivity showed greater benefits from various interventions (Tamagawa, Garland, Vaska, & Carlson, 2012), though similar research on breast cancer patients with depression is sorely needed; and (m) in several studies where nonsignificant effects of psychological interventions have been reported, limited sample sizes and diminished statistical power are evident such that larger samples may have produced significant treatment effects.

In conclusion, although the research is somewhat equivocal and in the context of described methodological limitations, data indicate that several psychological interventions may reduce depressive symptoms in breast cancer patients, with increasing support for third-wave behavioral therapies such as mindfulness-based and behavioral activation approaches. Given that studies have found depression to predict cancer incidence, progression, and mortality, and the (controversial) hypothesis that psychological interventions may increase survival time in breast cancer patients, methodologically sound research investigating the efficacy of psychosocial and pharmacological interventions for depressed breast cancer patients is a pressing need. Moreover, studies comparing the relative efficacy, feasibility, and cost-effectiveness of psychosocial and pharmacological treatment options for well-diagnosed depressed breast cancer patients are, in essence, nonexistent, and an important next step

in the research process. Therefore, although available treatment options for depressed breast cancer patients are plentiful, a more concerted and methodologically sound research effort is required before valid conclusions can be drawn about how to optimally reduce depression and improve the quality of life for depressed breast cancer patients.

Clinical Guidelines for Practitioners

Based on this review of the literature, a number of relevant guidelines can be offered to assist clinical practitioners working with breast cancer patients with depression. First, collaborative care generally is indicated such that a cooperative, multidisciplinary treatment team that includes, physicians, oncologists, nurses, and mental-health professionals is optimal in treating depressed breast cancer patients. The more effective the communication among these individuals, the better the continuity and comprehensiveness of care provided. Second, it is important to conceptualize depression on a continuum such that breast cancer patients may present with minimal, to modest and subthreshold depressive symptoms, to those with diagnosable MDD or dysthymia. Important differences and challenges exist within this structure, and for the latter group, a more intensive treatment plan may be required that potentially integrates both psychotherapy and pharmacotherapy. Third, although the research literature is imperfect from a methodological perspective, available evidence suggests that behavioral activation, mindfulness-based therapies, and problem-solving therapy have significant merit in the treatment of severely depressed breast cancer patients. Fourth, the advantages of individual psychotherapy over group psychotherapy are not clear in this context, and group treatment approaches thus may be the more cost-effective and practical option for clinicians. Indeed, interventions such as behavioral activation and SEGT have been effectively administered in this format. Fifth, the potential need for an integrated treatment approach for depression, such as psychotherapy and antidepressant medication should be monitored carefully by clinicians, particularly given the possible side effects, potential toxic interactions of cancer and antidepressant medications, and so forth. Sixth, the significance of social support in the lives of depressed breast cancer patients should not be underestimated. Given the co-existent medical and psychiatric conditions and associated stressors, social support offered by family, peers, and intimate partners is invaluable. Finally, as the course of MDD typically is more chronic with recurring episodes, following acute treatment, it is advisable to incorporate follow-up assessment and strategies to promote maintenance of treatment gains whenever feasible (e.g., psychotherapy booster sessions).

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CHAPTER

35 Cognitive Therapy for Comorbid Depression

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Abstract

Depression often co-occurs with other Axis I and Axis II psychiatric disorders. This chapter presents a model for how cognitive therapy (CT) of depression can be adapted in conceptualizing and treating the complex set of issues and problems that often accompany comorbid depression. It begins with a discussion of the prevalence of comorbidity in community and clinical samples, then reviews the research on comorbidity and outcome to CT for depression, followed by the presentation of a model for adapting or modifying CT for patients who present with depression and a comorbid Axis I or Axis II disorder. The chapter concludes with specific clinical guidelines for treating depression that co-occurs with anxiety disorders, substance use disorders, and personality disorders.

Key Words: cognitive therapy, depression, comorbidity, comorbid

One of the most efficacious and widely studied treatment of depression is cognitive therapy (CT; Beck, Rush, Shaw, & Emery, 1979) or what is often discussed under the generic label of cognitive-behavioral therapy (CBT). CT is grounded in an empirical and conceptual model that implicates certain underlying and maladaptive cognitive schemas as risk factors for depression onset and maintenance (Beck & Dozois, 2011; Clark, Beck, & Alford, 1999). Building on this model, the aim of the cognitive therapist is to work collaboratively with the patient to identify and modify negative cognitions, using specific strategies such as automatic thought monitoring and cognitive restructuring.

To date, there have been more than 75 clinical trials evaluating the efficacy of CT for depression. Results from these studies indicate that CT is an effective treatment for major depression and that it may have a prophylactic effect in reducing relapse and recurrence of depression (for reviews, see Beck & Dozois, 2011; Hollon, Thase, & Markowitz, 2002). A meta-analysis of 48 studies (N = 2,765 patients) found that CT was more effective in treating depression than waiting list or placebo (d = −0.82), antidepressants (d = −0.38), or therapies other than behavior therapy (d = −0.24); there was no difference in outcome between CT and behavior therapy (d = −.05) (Gloaguen, Cottraux, Cucherat, & Blackburn, 1998).

Despite its overall efficacy, however, not all depressed patients respond to standard CT for depression (for reviews of predictors of outcome to CT of depression, see Hamilton & Dobson, 2002; Whisman, 1993). Furthermore, most depressed patients in treatment present with complex sets of issues and problems that exacerbate, or are exacerbated by, their depressive symptoms. In particular, many depressed individuals experience depression that co-occurs with other Axis I or Axis II disorders. In this chapter, we present a model for conceptualizing and treating comorbid depression. We begin with a discussion of the prevalence of comorbidity in community and clinical samples, then review the research

on comorbidity and outcome to CT for depression, followed by a model for adapting or modifying CT for patients who present with depression and a comorbid Axis I or Axis II disorder, and conclude with some specific clinical guidelines for treating depression that co-occurs with anxiety disorders, substance use disorders, and personality disorders.

Depression Comorbidity

Depression often co-occurs with other Axis I disorders. For example, in the National Comorbidity Survey Replication (NCS-R), a population-based sample of 9,090 individuals 18 years or older from the 48 contiguous United States, 64% of people who met criteria for major depressive disorder during the year before the interview met criteria for at least one other Axis I disorder during the same 12 months (Kessler et al., 2003). Rates of comorbidity were 57.5% for anxiety disorders (i.e., generalized anxiety disorder, phobias, posttraumatic stress disorder, obsessive-compulsive disorder), 16.6% for impulse control disorders (i.e., bulimia, conduct disorder, oppositional defiant disorder, antisocial personality disorder, intermittent explosive disorder, pathological gambling), and 8.5% for substance use disorders (i.e., alcohol or drug abuse or dependence).

Compared with depressed individuals without comorbid conditions, those with comorbid Axis I disorders may be more likely to seek mental health services. For example, in the NCS-R, Axis I comorbidity was associated with a greater likelihood of receiving some type of mental health treatment in the year of the interview (Kessler et al., 2003), suggesting that the kinds of depressed patients that clinicians are likely to encounter are people with comorbid conditions. Indeed, comorbidity between major depression and Axis I disorders is high in clinical samples. For example, in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) effectiveness study of 2,876 outpatients with major depressive disorder who were treated in 23 psychiatric and 18 primary care settings, 65.2% of the sample met criteria for at least one comorbid Axis I disorder (Trivedi et al., 2006). Comorbidity with Axis II personality disorders is also likely to be high in treatment-seeking samples of depressed individuals. For example, in a large efficacy study that involved 180 depressed outpatients who were treated with medication or CT, 48% of patients met diagnostic criteria for at least one comorbid personality disorder (Fournier et al., 2008).

In sum, comorbidity is likely to be the norm rather than the exception among people with major depressive disorder, as evidenced both in epidemiologic and clinical samples. Depression comorbidity is not only common but also associated with greater severity. For example, Kessler, Chiu, Demler, and Walters (2005) used latent class analysis (LCA) to study comorbidity among the NCS-R disorders. Results indicated that a 7-class LCA model provided the best fit for the data, with one class representing highly comorbid major depressive episodes. With respect to severity, the majority (i.e., 70.5%) of people within this class were classified as serious (which was defined by criteria such as suicide attempt with serious lethality or work disability or substantial limitation), 28.1% were classified as moderate, and only 1.3% were classified as mild. Similarly, research with clinical samples of depressed individuals suggests that comorbidity is associated with greater severity (e.g., Smits, Minhajuddin, Thase, & Jarrett, 2012).

What are the clinical implications of depression comorbidity? At a minimum, comorbidity among depressed individuals is important insofar as patients with comorbid conditions seeking treatment for depression may be interested in treatment for their comorbid condition or conditions. For example, in a sample of people presenting for outpatient treatment with a principal diagnosis of major depressive disorder, 86.6% of people with at least one comorbid anxiety disorder wanted their treatment to address a comorbid anxiety disorder (Zimmerman & Chelminski, 2003). Furthermore, comorbidity among depressed individuals may be important insofar as comorbid conditions may complicate the presentation and treatment of depression. We turn now to a discussion of the implications of comorbidity for CT of depression.

Comorbidity and Outcome to CT of Depression

It is generally viewed that comorbid Axis I or Axis II disorders might result in poorer outcome to CT for depression. However, there has been surprisingly little research evaluating whether Axis I comorbidity is associated with poorer outcome. In the CT arm of the multisite Treatment of Depression Collaborative Research Project (TDCRP), treatment outcome was not associated with the presence of *double depression* (comorbid chronic minor depression or intermittent depressive disorder), although double depression was associated with poorer outcome when examined as a predictor across all patients in the TDCRP (Sotsky et al., 1991). Depressed patients with comorbid social phobia

tended to have poorer outcomes following CT in one study (DeRubeis et al., 2005), whereas another study found that the presence of comorbid social phobia was not associated with poorer outcome to CT for depression (Smits, Minhajuddin, & Jarrett, 2009). Finally, Smits et al. (2012) compared outcome following CT for depressed patients with or without high levels of anxiety symptoms and found that compared with nonanxious depressed patients, anxious depressed patients had lower response and remission rates based on clinician ratings; however, anxious depressed patients were found to improve more rapidly than nonanxious depressed patients in clinician-rated depression and expressed equivalent improvement to nonanxious depressed patients on self-report measures.

With respect to Axis II comorbidity, research support for an association between personality disorder and treatment outcome has been mixed. In the TDCRP, outcome for CT was not associated with the presence of comorbid personality disorders (Shea et al., 1990; Sotsky et al., 1991). Similarly, comorbid personality disorder was not significantly associated with outcome in a combined sample of patients who received either CT or medication (Fournier et al., 2008). In comparison, personality disorder was associated with a greater likelihood of premature dropout in a sample of patients treated with CT in private practice (Persons, Burns, & Perloff, 1988), and the presence of personality disorder was associated with poorer outcome following CT in a study of depressed outpatients treated in a community mental health center setting (Merrill, Tolbert, & Wade, 2003). Whereas these studies evaluated personality disorder in general, it may also be important to evaluate whether specific personality disorders are associated with outcome. Borderline personality disorder was associated with higher level of depressive symptoms at a 12-week evaluation in outpatients treated with CT, singly or in combination with medication (Burns & Nolen-Hoeksema, 1992). Because relatively few studies have been conducted that evaluate the association between personality disorders and outcome to CT of depression, it may be useful to consider that a meta-analysis of outcome across naturalistic and treatment studies found that compared with no personality disorder, comorbid personality disorder was associated with a doubling of the risk of poor outcome (Newton-Howes, Tyrer, & Johnson, 2006).

Furthermore, it may be that personality traits are associated with treatment outcome, even if a diagnosis of personality disorder is not. For example, in a review of personality pathology and treatment outcome in major depression, higher neuroticism scores generally predicted worse outcome, especially over long-term follow-up (Mulder, 2002); we are not aware of any studies that have evaluated the association between neuroticism and outcome to CT of depression. More relevant to cognitive case conceptualization, it may be that cognitions associated with personality disorder are predictive of outcome. Consistent with this perspective, a naturalistic study of depressed outpatients who were treated with CT found that whereas a diagnosis of personality disorder was not associated with outcome, greater endorsement of maladaptive avoidant and paranoid beliefs (but not dependent, obsessive-compulsive, and narcissistic beliefs) was associated with poorer outcome to CT (Kuyken, Kurzer, DeRubeis, Beck, & Brown, 2001).

In summary, there is some evidence that comorbid disorders, particularly comorbid personality disorders, are associated with poorer outcome to CT of depression, whereas other comorbid disorders do not appear to be associated with poorer outcome following CT. In evaluating the research on comorbidity and treatment outcome following CT for depression, it is worth noting that the impact of some comorbid disorders on outcome have been evaluated in only one study and other comorbid disorders have not been evaluated with respect to outcome. Furthermore, research on depression comorbidity and outcome is complicated by the fact that patients with comorbid disorders are often excluded from clinical trails evaluating the efficacy of CT for depression. Finally, this line of research is further complicated by the issue of statistical power: randomized clinical trails may not be adequately powered to test for predictors of outcome, particularly if they are categorical predictors such as the presence or absence of a comorbid disorder. In their meta-analysis of CT of depression, Gloaguen et al. (1998) reported that the mean sample size was 68. Assuming that half the patients in these trials received CT, this means that the average study included 34 patients who received CT. A sample size of 34 would provide adequate power (.80) for detecting only large effect sizes for continuous measures of comorbidity (e.g., symptom severity for comorbid anxiety) and even larger effect sizes for between-group comparisons involving categorical comorbid conditions (e.g., presence versus absence of a comorbid anxiety disorder) (Cohen, 1988). Therefore, sample size and statistical power should

be considered in interpreting the results of the studies that have evaluated the impact of comorbidity on outcome, particularly with respect to studies that have found no differences in outcome associated with comorbidity: it may be that in some cases the lack of differences may be due to insufficient statistical power.

Adapting CT for Comorbid Depression

In this section, we present a model for adapting CT to treat depression among people who have comorbid Axis I or Axis II disorders. In treating depression, it is important that clinicians assess the unique presenting problems and generate an individualized case conceptualization for each patient, representing a hypothesis about the mechanisms that underlie the patient's problems. Such hypotheses provide clues to the clinician as to what may be most relevant or clinically useful for the patient, and will guide selection of specific CT techniques to be used in the treatment. Further, as therapy proceeds, the case conceptualization provides a framework for hypothesis testing, and for refinement and revision of the treatment plan. In this section, we focus on case conceptualization in treating comorbid depression and how such a conceptualization can guide adapting and modifying CT of depression when working with people who have depression and comorbid Axis I or Axis II disorders. A more thorough description of these ideas and more extensive clinical guidelines for working with different comorbid conditions can be found in Whisman (2008).

Initial Assessment

Information obtained from an initial assessment can be useful in identifying the problems and issues that need to be addressed in treatment and in formulating recommendations about the most effective way to address these problems. There are several types of assessment methods that can be used for conducting an initial assessment for a patient presenting with depression. A comprehensive review of available measures is beyond the scope of this chapter, and the reader is referred to Joiner, Walker, Pettit, Perez, and Cukrowicz (2005) for a review of assessment measures of depression. Furthermore, a comprehensive assessment of Axis I disorders can be made through the use of a diagnostic interview such as the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), which is a semistructured interview that includes questions relating to specific symptoms that determine differential diagnoses. There are several versions of the SCID-I, including a shorter Clinician Version (SCID-CV; First, Spitzer, Gibbon, & Williams, 1997). The importance of using structured interviews in assessing Axis I conditions comes from research comparing comorbidity rates as determined through unstructured clinical interviews and structured research diagnostic interviews, which suggests that comorbidity is underdetected in unstructured interviews routinely used in clinical practice (Zimmerman & Chelminski, 2003; Zimmerman & Mattia, 1999).

There are also several interview and self-report instruments for assessing personality disorders, and the interested reader is referred to Widiger and Samuel (2005) for an overview of these instruments. The use of self-report measures to alert for the potential presence of personality disorders may be particularly useful in clinical settings, as completion of such measures requires minimal clinician time in administrating the measure; semistructured interviews could then be used to verify their presence.

Case Conceptualization for Comorbid Depression

There have been a number of different models proposed to account for comorbidity among psychiatric disorders, and the reader interested in systematic reviews of these models is referred to Neale and Kendler (1995). Although a full review of these models is beyond the scope of this chapter, we discuss several of the most commonly studied models of comorbidity. Specifically, given the focus of the chapter is on case conceptualization in CT for comorbid depression, we focus on the application of these models to cognitive factors in individuals with depression and comorbid conditions (for a more detailed description, see Whisman & Weinstock, 2008). According to cognitive theory of depression (Clark et al., 1999), maladaptive schemas are the underlying psychological mechanisms for depression and associated difficulties. The specific content of these schemas represent one's core beliefs: one's most central ideas about the self, the world/environment, and the future. Whereas cognitive theory is compatible with other models of vulnerability for depression, the theory proposes that these other factors are important in that they activate these latent maladaptive schemas. Thus, we focus our discussion on implications of comorbidity models as they may influence the activation of the cognitive mechanisms (i.e., maladaptive schemas) of depression.

The first model of comorbidity is a *correlated liabilities* model (Neale & Kendler, 1995), in which

comorbid conditions each have their own liability or vulnerability factor, but the liability or vulnerability factors are correlated (i.e., an increase in risk factors for one condition is associated with an increase in risk factors for another condition). As applied to cognitive theory of depression, the correlated liabilities model would suggest that depression and co-occurring conditions would each have their own cognitive vulnerability. Such a perspective is consistent with one of the basic tenets of cognitive theory, namely the cognitive *content specificity hypothesis*. According to this perspective, psychological disorders are distinguished by the form and content of their associated dysfunctional cognitions, beliefs, attitudes, and processes: "the key differences among the neuroses are revealed in the *content* of the aberrant thinking rather than in its form" (Beck, 1976, p. 82). The thought content associated with depression is believed to center on significant losses, particularly with reference to the loss of something considered essential to one's happiness. This can be contrasted with other disorders, such as mania, which is associated with an exaggerated positive view of self, world, and the future, or anxiety, which is associated with threat or danger. As reviewed elsewhere, there is considerable support for the content specificity hypothesis in terms of depression and anxiety (Beck & Perkins, 2001), although there has been less research evaluating specificity between depression and other disorders. Furthermore, although the content specificity hypothesis was originally proposed to account for differences in Axis I disorders, it has more recently been applied to Axis II disorders as well. That is to say, each personality disorder is hypothesized to have its own set of idiosyncratic set of beliefs and attitudes, which in turn give rise to the idiosyncratic behavioral patterns associated with that specific personality disorder (Beck, Freeman, Davis, & Associates, 2003). Support for this perspective comes from research showing that each personality disorder does indeed have a unique set of dysfunctional beliefs, and that these belief systems tend to be correlated with one another (Beck et al., 2001).

As applied to CT for comorbid depression, the cognitive content specificity hypothesis would predict that in some situations, a patient presenting with depression and a comorbid condition would have dysfunctional cognitions associated not only with depression but also with the content of each of the comorbid conditions. Thus, it would be expected that the cognitive content of a person with comorbid depression and anxiety would include both loss and threat, whereas a person with depression and a narcissistic personality disorder would include both loss and views of self as inferior and others as superior, hurtful, and demeaning. The implication of this model is that in such situations, CT with a patient with comorbid conditions may require targeting more beliefs than would be the case for someone with "pure" depression.

It should be noted that the cognitive content hypothesis was advanced to account for the differences between disorders, not to explain the comorbidity that occurs between disorders. However, we believe that this perspective can be expanded to account for comorbidity as well. Specifically, whereas each disorder may indeed have its own unique cognitive content, people that endorse one set of such beliefs are also likely to endorse other sets of beliefs. In other words, the degree or magnitude of endorsement of cognitive vulnerabilities for one disorder is likely to be correlated with the degree or magnitude of endorsement of cognitive vulnerabilities for another disorder. Therefore, comorbidity between depression and another condition in some situations could occur because the specific, underlying cognitive vulnerabilities for the two conditions are themselves correlated, which is what the correlated liabilities model of comorbidity hypothesizes. Support for this perspective comes from research finding correlations between cognitive contents associated with depression and anxiety (Beck & Perkins, 2001) and among the cognitive contents of different personality disorders (Beck et al., 2001).

The second comorbidity model is an *alternate forms* model (Neale & Kendler, 1995), in which comorbid conditions are alternate manifestations of a single liability or vulnerability factor. According to this model, comorbid conditions share a single vulnerability factor. A common example of an alternate forms model advanced to account for the comorbidity between depression and anxiety is the recently updated tripartite model—the revised integrative hierarchical perspective—which hypothesizes that depression and anxiety share a common higher-order vulnerability of trait negative affectivity, and the related personality trait of neuroticism (Mineka, Watson, & Clark, 1998).

As applied to the cognitive model of depression, there may be cognitive vulnerability factors that give rise both to depression and to comorbid conditions. A. T. Beck (1983) identified two cognitive-personality styles that are hypothesized to reflect distinct underlying themes that are associated with major depression—*sociotropy*,

or excessive need for approval from others, and *autonomy*, or excessive concern about independent achievement. Sociotropy and autonomy correspond to the core beliefs of unlovability and worthlessness, respectively, which are the two broad categories of core beliefs associated with psychopathology (Beck, 1995). The introduction of these two dimensions represents a shift in the evolution of cognitive vulnerabilities for depression, as cognitive theory for depression before this time had focused more on specific idiosyncratic negative schemas (Clark et al., 1999). Although initially proposed as vulnerabilities to depression, research has shown that sociotropy and autonomy are also associated with other Axis I disorders, including anxiety (e.g., Alford & Gerrity, 2003) and bulimia (e.g., Hayaki, Friedman, Whisman, Delinsky, & Brownell, 2003), and with personality disorders (Ouimette, Klein, Anderson, Riso, & Lizardi, 1994). Thus, there is emerging evidence that sociotropy and autonomy may represent broad-based cognitive vulnerabilities that could give rise to depression and other disorders, which would be consistent with the alternate forms model of comorbidity.

As applied to CT for comorbid depression, the alternate forms model of comorbidity would suggest that in some situations, comorbid conditions would have a common, underlying cognitive vulnerability with depression. In support of this perspective, cognitive risk factors for depression (i.e., negative inferential style and dysfunctional attitudes) are also associated with the presence of Axis II diagnoses and dimensional scores of personality disorder pathology among people who did not meet criteria for current Axis I disorders, suggesting that depression and personality disorder share common cognitive risk factors (Smith, Grandin, Alloy, & Abramson, 2006). The implication of this model is that treating the common underlying cognitive mechanism should help reduce depression and the comorbid condition(s).

A final comorbidity model is the *causation* model (Neale & Kendler, 1995). In this model, one condition has a direct influence on the development of another condition or the two can directly influence each other in a reciprocal fashion. In discussing causation models, it is important to consider the temporal ordering of onset of depression relative to other conditions. In a large, representative community survey, it was found that lifetime cases of depression were most often secondary to other Axis I disorders, with anxiety disorders being the most common primary disorders associated with secondary depression (Kessler et al., 1996). These findings are important in suggesting that depression may, in many cases, be secondary to other Axis I psychiatric disorders. Furthermore, it was found that secondary depression was more severe and persistent than primary or pure depression.

As applied to cognitive theory of depression, there have been relatively few causation models advanced to account for the comorbidity between depression and other conditions. One notable exception is a model proposed by Alloy, Kelly, Mineka, and Clements (1990) to account for the comorbidity between depression and anxiety. According to this model, depressive and anxiety disorders share a cognitive vulnerability of expectation of uncontrollability (i.e., an expectation of helplessness), but depression occurs only when helplessness turns into hopelessness. Specifically, this model suggests that people who expect to be helpless in controlling important future outcomes but are unsure of their helplessness will exhibit anxiety. If they then become convinced of their helplessness, but are still uncertain about the future likelihood of negative events, they will experience mixed anxiety and depression. Finally, if the perceived probability of future negative events becomes certain, then helplessness becomes hopelessness and they exhibit depression.

As applied to CT for comorbid depression, the causation model of comorbidity would suggest that in some situations, comorbid conditions may be a cause of depression (i.e., primary), whereas in other situation they could be a consequence of depression (i.e., secondary). As such, this model may suggest that treating the primary condition may enhance the impact of treatment for the secondary condition. For example, if an anxiety disorder was conceptualized as occurring before the onset of depression, addressing this disorder first may result in reductions in depression or may make it easier to conduct CT for depression.

There are other comorbidity models in addition to these three models (Neale & Kendler, 1995). For example, it may be that comorbidity is a separate disorder (or a subtype of one of the disorders), with a liability or vulnerability that is independent from either disorder. Because these models do not easily map onto cognitive theory of depression, they will not be discussed here.

In summary, there are at least three ways of conceptualizing comorbidity that may occur between depression and other conditions. Each model has its

own implications for how CT may be conducted to most effectively deal with depression co-occurring with other conditions. Consequently, using these frameworks to conceptualize a particular patient's comorbid conditions might help to guide treatment planning. For example, a clinician might intervene differently when comorbid conditions reflect a co-occurrence of independent disorders versus a common underlying etiology versus a causal association between disorders.

Adapting CT in Treating Comorbid Depression

Having discussed assessment and conceptualization of comorbid depression, we turn our attention to ways of tailoring CT for comorbid depression. In this section, we present a framework for ways in which CT could be adapted or modified in treating comorbid depression.

MODIFYING THE PARAMETERS OF TREATMENT DELIVERY FOR CT OF DEPRESSION

Based on the case conceptualization, therapists might choose to modify the parameters under which CT is administered. Specifically, based on the case conceptualization, a therapist might choose to modify the length of treatment. For example, Smits et al. (2012) suggest that depressed patients with high levels of comorbid anxiety symptoms may require additional time or more sessions to achieve remission relative to nonanxious depressed patients. Similarly, strong endorsement of negative schema, characteristic of depressed individuals with comorbid personality disorder, might require that treatment be extended to provide a greater number of opportunities for testing out alternative belief systems. Alternatively, the therapist might choose to modify the frequency and timing of sessions. For example, Thase et al. (1994) reported that chronically depressed and acutely depressed individuals diverged in recovery when therapy sessions changed from twice weekly to once per week; similarly, depressed patients with comorbid disorders may require more frequent sessions than the typical weekly sessions.

MODIFYING THE STYLE OF PRESENTATION FOR CT OF DEPRESSION

Another potential way of modifying treatment concerns the style or manner of conducting CT. That is to say, there may be individual differences in preference and responsiveness to different types of CT interventions. For example, the underlying personality characteristics of sociotropy and autonomy are believed to be associated with how depressed individuals will respond to different aspects of treatment. This has been labeled the *differential treatment hypothesis* (Clark et al., 1999). According to A. T. Beck (1983), patients who are high in sociotropy will prefer and be more responsive to interventions that emphasize support, helping, and emotional closeness. It is hypothesized that these individuals are likely to prefer an informal and closer relationship with their therapist and may rely on him or her to help solve their problems. In comparison, patients who are high in autonomy will prefer and be more responsive to goal-directed, task-focused, and problem-oriented interventions. It is hypothesized that these individuals are likely to prefer a more formal, detached relationship with their therapist, and are likely to respond to a collaborative relationship in setting the agenda, selecting topics for each session, and assigning homework.

Research on the differential treatment hypothesis has focused on whether sociotropy and autonomy are associated with differential treatment response to pharmacotherapy or group versus individual CT (Clark et al., 1999). As such, there is little empirical evaluation for whether tailoring treatment focus and therapist style based on a patient's level of sociotropy or autonomy is associated with preference and response to CT of depression, although this would be an important and clinically informative area for future research.

MODIFYING THE EMPHASIS OR FOCUS OF CT OF DEPRESSION

Another direction for modifying CT of depression is to emphasize or place a greater focus on one or more specific aspects of CT of depression. For example, Beck et al. (1979) hypothesized that greater severity of depression would require greater use of behavioral strategies in CT. Therefore, whereas behavioral interventions might be included in working with many depressed individuals, they may make up a larger percentage of sessions for people who are more severely depressed, such as people with comorbid disorders. Other authors have suggested that the efficacy of CT for severely depressed patients (e.g., patients with comorbid depression) could be maximized by emphasizing homework assignments (Persons et al., 1988).

Another area in CT for depression that might be emphasized in working with patients with comorbid depression is differing emphasis on the therapeutic alliance. Although theorists differ somewhat in their

definition of the therapeutic alliance, most definitions include the following three components: a bond between the patient and therapist, an agreement on treatment goals and tasks, and a collaborative relationship (for a review, see Martin, Garske, & Davis, 2000). A good therapeutic alliance is viewed as necessary but not sufficient in conducting CT for depression (Beck et al., 1979). Indeed, research has shown that a better therapeutic alliance predicts a better outcome in CT of depression, although the effect sizes obtained in prior research have been modest (Persons & Burns, 1985); similarly, there is a small but reliable association between the therapeutic alliance and a variety of outcomes following psychotherapy in general (for a meta-analysis, see Martin et al., 2000).

There are two corollaries that follow from evidence that the therapeutic alliance is associated with outcome for depressed patients receiving CT. First, patient, therapist, and other factors that hinder the development of the therapeutic alliance should result in poorer outcome to CT. Comorbid conditions may be one set of factors that are associated with poorer therapeutic alliance. For example, a depressed patient with social anxiety disorder or dependent personality disorder might be less likely than a patient without either of these comorbid conditions to ask a clinician for help with a comorbid condition or disagree with a clinician about his or her case conceptualization or treatment plan due to fear of negative evaluation by the clinician; both of these comorbid conditions could therefore adversely affect the patient and therapist's agreement on goals and tasks. Similarly, a therapist conducting CT with a depressed patient with avoidant or paranoid beliefs (Kuyken et al., 2001) or a personality disorder such as borderline personality disorder (Lee & Overholser, 2004) might have a more difficult time forming a bond than he or she would with a depressed patient without such a comorbid condition, given that difficulty in interpersonal relationships is a defining feature of personality disorder.

The second corollary that follows from evidence that the therapeutic alliance is associated with outcome for depressed patients receiving CT is that clinical interventions that improve the therapeutic alliance should improve outcome. Therefore, if a clinician believes that a comorbid condition is adversely affecting the therapeutic alliance, then the clinician might want to devote more effort at improving the alliance than the clinician would with someone without a comorbid condition. For example, a clinician working with a depressed patient with comorbid borderline personality disorder may want to make sure to validate the patient, particularly in the early stages of therapy, and not rush into challenging the patient's cognitions prematurely (Lee & Overholser, 2004; Robins, Fenwick, Donnelly, & Lacy, 2008). Furthermore, the therapeutic relationship may be used as a testing ground for modifying cognitions, particularly for patients with personality disorders or dysfunctional personality traits (Beck et al., 2003; Young, Klosko, & Weishaar, 2003).

AUGMENTING STANDARD CT OF DEPRESSION

A final method for modifying CT of depression is to supplement standard treatment with additional treatment interventions. From a theoretical perspective, interventions that are compatible with the cognitive theory of depression (i.e., the theory that maladaptive information processing is central to understanding the onset, course, and treatment of depression; Clark et al., 1999) can be appropriately considered as cognitive in nature (Whisman, 1999). That is to say, it is compatibility with cognitive theory, and not whether an intervention is labeled a "cognitive" intervention (versus a behavioral or interpersonal intervention), that "provides a unifying theoretical framework within which the clinical techniques of other established, validated approaches may be properly incorporated" (Alford & Beck, 1997, p. 112). From this perspective, there are many different types of intervention that could be added to standard CT of depression that could be useful in modifying maladaptive information processing.

For some patients, adding one or several specific interventions for a comorbid condition may improve outcome for depressed individuals with comorbid conditions. For example, emotion regulation skills and distress tolerance skills from dialectic behavior therapy (DBT; Linehan, 1993) might be incorporated in CBT for a patient with depression and comorbid borderline personality disorder to help the patient better manage his or her negative thoughts, emotions, and behaviors (Lee & Overholser, 2004; Robins et al., 2008). For other patients, entire treatment protocols might need to be integrated into CT for depression to address the comorbid condition. For example, a depressed patient with a comorbid specific phobia might need a full regimen of systematic desensitization to overcome her fear of flying.

Modifying standard CT of depression with supplemental interventions generally proceeds in one of two directions. First, therapists might use additional

clinical techniques in targeting other problems in a sequential fashion. Treating one disorder and then the other disorder may be indicated in situations in which the clinician believes that the two conditions are simply contemporaneous (i.e., that one condition is not causing the other condition), as would be suggested by the correlated liabilities model described earlier. In deciding on the order of treatment, the clinician may want to consider which problem is most severe or most distressing to the patient and begin with the most severe or distressing problem. Another approach to sequencing treatment strategies is to begin with the problem that is seen as primary (i.e., occurring before other problems), subsequently moving to secondary problems once the primary problem is successfully treated. For example, if a patient is depressed because he or she is housebound due to preexisting agoraphobia, it may be beneficial to first target the agoraphobia before targeting the patient's depression. Furthermore, if one problem is causing the other problem (as suggested by the causation model presented earlier), then treating the primary problem may alleviate the secondary problem.

In comparison to sequential treatment, there may be occasions in which CT treatment interventions are provided simultaneously within a session or across several sessions. For example, in cases where depression and another disorder are equally distressing to the patient, targeting the two conditions might alternate from one session to the next. Thus, sessions focusing on CT interventions targeting depression could be alternated with sessions focusing on CT interventions targeting the other disorder. As an example of this approach, Kush (2004) presented a CT approach for treating mixed depression and anxiety in which she recommends simultaneously treating depression and anxiety, with the allocation of session time divided between the two conditions based on which one is most acute in a particular session. However, Gibbons and DeRubeis (2008) reported that the amount of time and effort spent addressing anxiety in sessions of CT of depression predicted less improvement both in depression and anxiety symptoms over the course of treatment. They discussed several potential explanations for this finding, including that therapists were diverted from depression treatment by anxiety symptoms (potentially due to patient factors) or that treatment of both symptoms concurrently sends multiple messages to patients resulting in patients becoming confused about how to implement different methods for dealing with their depression and anxiety. These results underscore the need for a clear case conceptualization of any comorbid conditions, as well as the importance of clear communication between the therapist and patient about the goals and objectives for treatment interventions targeting comorbid conditions.

A third approach to supplementing standard CT of depression would involve developing a treatment that specifically addresses a particular manifestation of depression. Thus, unlike a treatment that focuses on independent forms of intervention that are presented in a successive or alternating fashion, such a modification would reflect the development of a different treatment protocol that would be delivered for a particular manifestation of depression. In this case, the treatment shares the theoretical underpinning of CT for depression, as well as some common interventions, but the resulting treatment may be different enough to be considered its own treatment. For example, depressed individuals with comorbid suicidal ideation may be one example of a manifestation of depression that requires its own type of CT protocol (for a CT protocol for treating suicide, see Ghahramanlou-Holloway, Brown, & Beck, 2008).

Adapting CT for Depression for Specific Comorbid Conditions

Having presented an overview of general principles for adapting CT for depression for patients with comorbid Axis I or Axis II disorders, we turn now to a discussion of clinical guidelines for treating depression that is comorbid with personality disorders and several common, specific Axis I disorders.

ANXIETY

In working with depressed patients with comorbid posttraumatic stress disorder, generalized anxiety disorder, or obsessive-compulsive disorder, an important underlying feature of both the anxiety disorder and depression tends to be repetitive, ruminative thoughts. These thoughts typically revolve around a sense of uncertainty (leading to anxiety) and helplessness (leading to depression). Therefore, in working with individuals who are comorbid for these anxiety disorders, it may be helpful to specifically target the repetitive nature of these thoughts, as doing so may help patients simultaneously reduce symptoms of depression and anxiety (Singer, Dobson, & Dozois, 2008). Additionally, when working with individuals with comorbid PTSD and depression, negative or traumatic life events tend to precipitate the onset of both disorders.

Therefore, the therapist may want to initially focus more on cognitive restructuring around dysfunctional meaning or attributions attached to these events, which may have shared underpinnings (Singer et al., 2008). Individuals with anxiety and depression tend to overestimate the probability and severity of threats and underestimate their ability to cope with these threats. Therefore, the target of treatment is to help the patient develop a healthier, evidenced-based balance between assessment of threats and self-perceived ability to cope effectively with them.

Singer et al. (2008) suggest that it may be useful for therapists treating primary depression (with comorbid OCD, PTSD, or GAD) to apply a behavioral activation approach, which focuses on graded activities to increase rewarding experiences. First, the therapist helps the patient understand the connection between mood and behavior, with particular emphasis on the role avoidance plays in reducing the frequency of rewarding experiences. Achievable activities are then scheduled that increase the patient's feelings of pleasure (e.g., going for a walk) and mastery (e.g., paying bills), while at the same time looking for opportunities to design activity homework that is simultaneously effective for the comorbid disorders (e.g., taking a bath can be both pleasurable and relaxing, or making a schedule for the week can provide a sense of mastery and reduce anxiety through organization). Additionally, exposure activities are particularly beneficial for reducing anxiety and also lead to feelings of mastery.

Otto, Powers, Stathopoulou, and Hofmann (2008) recommend that when treating depression with comorbid anxiety disorders, such as panic disorder and social phobia, therapists focus on three important sources of negative affect that are adversely influenced by the comorbid anxiety disorder. First, they advise addressing fears of anxiety sensations or feared situations (such as occur with social phobia or agoraphobia) that increase the difficulty of completing potentially helpful behavior tasks. Second, perceptions of failure in these activities, which can even be elicited by anxiety sensations, may increase negative self-evaluations and depressed affect. This can attenuate the naturally arising positive affect that results from engaging in rewarding activities. Third, erroneous cognitive evaluations of failure due to anxiety or avoidance may confirm or even increase beliefs that the person is flawed or incompetent. To address these potential complications, effective treatment should assess how much anxiety the patient is likely to feel and his or her likelihood of avoiding homework tasks, followed by collaboratively ensuring behavioral experiments are sufficiently graded. The therapist and patient should then ensure anxiety/avoidance-specific cognitions are addressed in advance by developing and rehearsing alternative responses, so as to inoculate the patient against self-perceived failure or coping through avoidance.

With regard to ordering treatment, Otto et al. (2008) suggest (a) that the therapist and patient seek to understand the patient's perception of which symptom clusters are most relevant to their distress; (b) conduct a functional analysis of the causal pattern between the patient's anxiety, avoidance, and depression; (c) ensure a step-by-step continuity in treatment by reviewing the previous session's progress and integrating any current distress into the overall focus on treatment of core maladaptive patterns (rather than becoming derailed by the "crisis of the week"); and (d) capitalize on early gains as a source of motivation by highlighting the link between the patient's efforts and his or her improvements.

SUBSTANCE USE DISORDERS

Newman (2008) identified four important considerations for adapting CT for treating depression comorbid with substance use disorders. First, patients may be unwilling to acknowledge that their substance use is problematic or that it is a contributing factor in their depression, and questions from the therapist may elicit resistance or defensiveness. Second, substance abuse between sessions may interfere with implementing skills learned in session and the completion of homework assignments. Third, patients may harbor the belief that they are treating their symptoms of depression with the use of alcohol or drugs. Therefore, they may be reluctant to give up these forms of self-medication. Fourth, patients may misuse principles of 12-step programs to argue against the CT model.

To address the first of these, a client's resistance to discuss their substance abuse, Newman (2008) suggests that patients who might otherwise benefit from therapy may withdraw from treatment if the therapist demands the patient receive substance abuse treatment before any other treatment will be considered. Rather, he proposes the usefulness of adopting Prochaska, DiClemente, and Norcross' (1992) *stages of change model*, in which it is important to recognize the client's current level of readiness to make changes to their substance use. In doing so, the therapist does not complicity agree to

ignore the substance abuse but rather focuses more on building a therapeutic alliance, working to alleviate symptoms of depression, and continuing to assess the client's readiness to address the substance abuse in hopes that the client may become better socialized into the therapy process and more willing to address their substance abuse later in treatment once a more solid treatment alliance has been established. There is an understandable dilemma for therapists in treating a patient for depression while allowing the substance abuse to temporarily not be a focus of treatment. Some treatment models would stipulate that a patient must first receive substance abuse treatment before any additional treatment can be conducted or at least be a co-target from the start or therapy. This may be the most appropriate course of action in many cases; however, the advantage of taking a more flexible approach is that it encourages a patient to participate in treatment who might otherwise drop-out, and by treating the depression, the motivation to abuse substances may decline and the patient may become ready to discuss substance use issues with the therapist.

With respect to the issue that patients' substance use can inhibit their use of skills outside of session, Newman (2008) recommends the therapist may want to help patients develop preemptive strategies such as audio recordings of relevant skills to use or encouragements, written reminders, or other such devices as coping strategies for the client when they are intoxicated or about to use a substance. It may be easier for people to use these passive recall tools rather than having to free-recall their therapy skills at times when their ability to think may be compromised by a substance or the craving for the substance.

To address patients' belief that the substance of abuse is an effective self-medication for their depression, Newman (2008) recommends educating patients on the vicious cycle created by the interplay between depression and substances, including the physiologically depressive effects of alcohol or the effects of withdrawing from a drug. The therapist may suggest patients gather data about the relationship between their substance use and their mood. For example, patients could rate their mood before drinking, after drinking, and then the following morning. Additionally, it is important that the therapist work with the patient to collaboratively identify more effective ways of coping with emotional distress that do not involve drinking or using drugs.

Finally, Newman (2008) observes that 12-step programs can be a useful option that compliments individual CT by providing guiding principles for recovery as well as social support for patients who may have little in their life (a common problem in both depression and substance abuse). However, cognitive distortions, rationalizations, or misinterpretations may occur with regard to the principles of a 12-step program. For example, the first of the 12-steps is admitting powerlessness in the face of the disease of addiction, which with some all-or-nothing thinking, can be misinterpreted as an inability or excuse for not working to develop new skills or implement new behavior. The therapist can work with the patient to develop greater cognitive flexibility in order to better understand the repeated failures of the previous coping style in the face of addiction (i.e., powerlessness) while still engendering a sense of self-efficacy to make changes and learn new ways of coping.

PERSONALITY DISORDERS

Working with an individual with depression and a comorbid personality disorder can be very challenging to a therapist when deciding where to begin treatment. The depression tends to exacerbate the features of the personality disorder and the features of the personality disorder are quite often contributing to and reinforcing the depression. Freeman and Rock (2008) advise that the therapist treat the depression first. The rationale for this is several-fold. Specifically, patients most likely entered therapy in order to alleviate symptoms of depression rather than personality disorder; treatment of depression, therefore, becomes the primary treatment contract. Next, depression is more likely to improve with treatment and will do so more quickly than treatment for a personality disorder. Improvements in symptoms of depression are also likely to benefit the maladaptive features of a personality disorder. Additionally, given the complexity of treating personality disorders, most therapists are likely to be better trained and thus more effective at treating depression. Finally, many of the CT skills patients develop through working on their depression can then be applied to the more complex and pervasive features of a personality disorder. This is not to say that the personality disorder need be ignored, but rather treated as a secondary focus of treatment. For instance, the therapist could include an emphasis on skills such as emotional tolerance and mindfulness in the work with depression if the individual also has comorbid borderline personality disorder.

Once the symptoms of depression improve, the target of treatment can shift towards core schemas,

as they relate to the personality disorder and the depression (Freeman & Rock, 2008). For each of the personality disorder clusters, there are different ways in which the personality disorder and depression are likely to interact in creating the client's unique set of distressing symptoms. For example, patients with a Cluster C personality disorder such as avoidant personality disorder, may be experiencing greater depression due to their predisposition towards feeling anxious in social situations and withdrawing from interpersonal contact, despite wishing for more relationships. Depression may arise from the client's self-imposed isolation and be the result of schemas that, for example say, "People are judgmental" or "I am not worthy of other's affection." As the therapist begins to tackle the depression-relevant features of the personality disorder, he or she may find it to be helpful to be thinking in terms of the client's predominant schemas about the self, world, and future, and use this as a guiding framework for understanding the context in which the depression is occurring.

In working with individuals with comorbid depression and borderline personality disorder, Robins et al. (2008) suggest ways to incorporate features of DBT (Linehan, 1993) to conceptualize treatment goals. Within this model, Stage 1 of treatment would focus on the most severe, quality-of-life concerns and therapy interfering behaviors. Depending on severity, depression will likely be a core focus of the Stage 1 treatment, along with suicidality, self-injurious behavior, and therapy interfering behavior. Once attending to these more immediate treatment demands, CT can then focus on distorted cognitions and maladaptive patterns of behavior. They recommend a different approach to working with cognitions than might be done in standard CT. Namely, instead of immediately testing the accuracy of thoughts, clinicians working with depressed individuals with comorbid borderline personality disorder may want to repeatedly call the patient's attention to the concept that thoughts are just thoughts, not facts. This emphasizes a decentered approach to thoughts that may increase cognitive flexibility and willingness to challenging these thoughts later on; otherwise, the therapist may experience backlash from the patient due to what may be misperceived as invalidation of the patient's perspectives from the therapist.

Conclusion

Major depressive disorder often co-occurs with one or more Axis I clinical conditions or Axis II personality disorders. Because of high rates of comorbidity, "pure" cases of depression are not only relatively rare but may also be unrepresentative of people with depression, particularly with respect to depressed individuals in treatment. Depressed individuals who have comorbid conditions may have more severe depression, may desire treatment for the co-occurring disorder, and may have poorer outcome to CT. The relative rarity of cases that meet criteria for the single diagnosis of major depression and the clinical impact of comorbidity on treatment planning and treatment outcomes suggests the need for incorporating comorbidity into the way depression is conceptualized and treated. In this chapter, we have presented a model for conceptualizing and treating comorbid depression in the context of CT. Clinical trials are needed to evaluate the efficacy and effectiveness of CT for comorbid depression, as comorbidity is likely to be the rule rather than the exception among depressed patients seen in clinical practice.

Although we have focused on comorbidity between depression and Axis I and Axis II disorders in this chapter, it is important to note that depression often co-occurs with other conditions that may complicate treatment and impact treatment outcome. For example, as reviewed elsewhere (e.g., Beach & Whisman, 2012), how well people are functioning in their intimate relationships (e.g., marriage) is associated with the onset, course, and treatment of depression. Specifically, there is a high rate of co-occurrence between depression and relationship discord (e.g., Whisman, 2007), and relationship discord is associated with poorer outcome to treatments for depression (e.g., Whisman, 2001). With respect to CT for depression, patients who believe that the cause of their depression is due to marital problems are less likely to engage in homework (Addis & Jacobson, 1996) and those that believe that their marital problems preceded their depression have poorer outcomes following CT of depression (O'Leary, Riso, & Beach, 1990). Although a discussion of comorbidities other than Axis I and Axis II disorders is beyond the scope of this chapter, the model presented in this chapter can be applied to other comorbid conditions; clinical guidelines for adapting CT for depression for patients with other comorbid conditions, including marital and family problems and medical conditions, can be found in Whisman (2008).

It is also important to note that we have focused on the cognitive assessment, conceptualization, and treatment of depressed patients who have a comorbid Axis I or Axis II disorder and seek treatment

primarily for their depression. Depression can also co-occur with Axis I disorders among patients who seek treatment primarily for these other Axis I disorders. However, a discussion of depression comorbidity for people who primarily present for treatment for these other disorders is beyond the scope of this chapter.

It is hoped that assessing for comorbid conditions and adapting standard CT of depression based on the conceptualization of each patient's depression based on the results of that assessment will result in improved outcome. It is further hoped that continued developments in the conceptualization, design, and sequencing of CT interventions for the varying, and often challenging, presentations of depression comorbidity will also serve as a foundation for further developments in cognitive and other theories of depression comorbidity.

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CHAPTER

36 The Big Picture

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Abstract

This chapter begins with an overview of epidemiological research on comorbidities between major depression and other mental disorders. We emphasize the potential value of future studies building on recent evidence of the importance of latent liabilities in investigating the dynamics of comorbidities between depression and temporally primary and secondary mental disorders. We then turn to an overview of epidemiological and clinical research on comorbidities between major depression and a number of chronic physical disorders. We emphasize the potential value of expanding the number of mental disorders in future studies of this sort to include those known to be highly comorbid with major depression, so as to distinguish between mental/physical comorbidities specific to major depression and those involving a broader latent liability.

Key Words: comorbidity, latent liability, major depression, chronic physical disorders, primary and secondary disorders

As previous chapters in this volume make clear, major depression is a commonly occurring and seriously impairing disorder that is linked to diminished role functioning and quality of life, high rates of both mental and physical comorbidity, and early death (Bromet, Andrade, Hwang, Sampson, Alonso, et al., 2011; Kessler, 2012; Moussavi, Chatterji, Verdes, Tandon, Patel, et al., 2007; Üstün, Ayuso-Mateos, Chatterji, Mathers, & Murray, 2004). In thinking about the issue of comorbidity, two *big picture* facts become immediately apparent from cross-national epidemiological data. First, major depression is highly comorbid with a wide range of other mental (Kessler, Ormel, Petukhova, McLaughlin, Green, et al., 2011) and chronic physical disorders (Kessler, Birnbaum, Shahly, Bromet, Hwang, et al., 2010). Any theorizing or empirical analysis about comorbidity in major depression must take this great range of associations into consideration. Second, the age-of-onset (AOO) distribution of major depression, although quite wide, shows that the vast majority of lifetime cases begin at a later age than many comorbid mental disorders and at an earlier age than most comorbid physical disorders (Kessler, Amminger, Aguilar-Gaxiola, Alonso, Lee, et al., 2007). This temporal sequence must be taken into consideration in thinking about the relative importance of major depression as a risk for and consequence of comorbid disorders.

The first of these two facts is especially important for research on comorbidity between major depression and chronic physical disorders because the vast majority of empirical research on the associations of depression and physical disorders has treated depression as the only mental disorder of interest rather than considering parallel associations with other mental disorders (e.g., Anderson, Freedland, Clouse, & Lustman, 2001; Currie & Wang, 2004; Dickens, Jackson, Tomenson, Hay, & Creed, 2003). One of the few empirical studies that examined a

broader set of comorbidities notes that this focus "may lead to a relatively narrow explanation of the nature of the comorbidity" (Gureje, 2009). Based on this fact, we begin the current chapter by discussing recent literature on comorbidities of major depression with other mental disorders. We then turn to consider research on comorbidities of major depression with physical disorders based on an awareness that the mental disorders known to be strongly associated with major depression have seldom been considered in the latter studies.

Comorbidities of Major Depression with Other Mental Disorders

Basic Patterns of Comorbidity

Comorbidity is the norm among common mental disorders, as more than 50% of people with one of the mental disorders typically assessed in community epidemiological surveys in a given year have multiple disorders (Demyttenaere, Bruffaerts, Posada-Villa, Gasquet, Kovess, et al., 2004; Kessler, Chiu, Demler, Merikangas, & Walters, 2005). Major depression is no exception to this rule. This is illustrated in the World Health Organization (WHO) World Mental Health (WMH) Surveys. The WMH surveys are a series of community epidemiological surveys of mental disorders in more than two dozen countries throughout the world (Kessler & Üstün, 2008). In those surveys, 56.3% to 62.0% of respondents in developing and developed countries who had a DSM-IV major depressive episode at some time in the 12 months before the survey also met criteria for at least one of the other DSM-IV disorders assessed (Kessler, Birnbaum, Shahly, Bromet, Hwang, et al., 2010). The odds ratios (ORs) of these proportions among survey respondents with as opposed to those without 12-month major depressive episodes were between 8.1 and 12.6; that is, the odds of comorbidity were these many times as high among respondents with than those without 12-month depression. Furthermore, these comorbidity ORs increased as the number of comorbid disorders increased, from 5.7 to 7.8 for having exactly one comorbid disorder and 14.1 to 21.2 for having exactly two comorbid disorders to 28.5 to 55.4 for having three or more comorbid disorders.

The Factor Structure of Comorbidity

The structure of comorbidity among common mental disorders has been the subject of considerable interest over the past decade. Beginning with an influential paper by Krueger (1999), numerous researchers have used factor analysis to document that associations among hierarchy-free anxiety, mood, disruptive behavior, and substance use disorders can be accounted for by correlated latent predispositions to internalizing (anxiety, mood) and externalizing (disruptive behavior, substance) disorders. The internalizing dimension is sometimes further divided into secondary dimensions of fear (e.g., panic, phobia) and distress (e.g., major depressive episode, generalized anxiety disorder) (Beesdo, Bittner, Pine, Stein, Hofler, et al., 2007; Cox & Swinson, 2002; Krueger & Markon, 2006a; Lahey, Rathouz, Van Hulle, Urbano, Krueger, et al., 2008; Slade & Watson, 2006; Vollebergh, Iedema, Bijl, de Graaf, Smit, et al., 2001). These results have been used to argue for a reorganization of the classification of mental disorders in the DSM and ICD diagnostic systems (Andrews, Goldberg, Krueger, Carpenter, Hyman, et al., 2009; Goldberg, Krueger, Andrews, & Hobbs, 2009; Krueger & Markon, 2006b; Watson, 2005; Wittchen, Beesdo, & Gloster, 2009), although other data suggest that this theoretical structure might be insufficiently robust to serve as the basis for such a reorganization (Beesdo et al., 2009; Wittchen, Beesdo-Baum, Gloster, Hofler, Klotsche, et al., 2009). For example, the distinction between fear and distress disorders does not emerge in all studies (Beesdo et al., 2009; Krueger, Caspi, Moffitt, & Silva, 1998; Krueger & Finger, 2001; Wittchen, Beesdo-Baum, et al., 2009), and model fit deteriorates when additional disorders are added or when the model is estimated separately among people at different life-course stages (Watson, 2005; Wittchen, Beesdo-Baum, et al., 2009).

Despite these inconsistencies, the general finding of strong comorbidity within the internalizing and externalizing domains has raised the question whether common risk factors exist for the disorders in either of these domains, and if so, whether risk factors for individual disorders documented in previous studies are actually risk factors for these broader predispositions. As noted in the introduction, the issue of specificity versus generality of risk factors is of considerable importance, as a number of hypotheses about causal pathways posit the existence of very specific associations between particular risk factors and particular outcomes. These interpretations would be called into question if empirical research showed that the risk factors had less specific predictive effects (Green, McLaughlin, Berglund, Gruber, Sampson, et al., 2010). In addition, evidence that a risk factor had a broad effect on a wide range of disorders would increase interest

in that risk factor as an intervention target (Mrazek & Haggerty, 1994).

Although the use of latent variable models to study risk-factor specificity is only in its infancy, research has already shown that this line of analysis has considerable value in distinguishing specific versus nonspecific risk factors. For example, Kramer and colleagues (Kramer, Krueger, & Hicks, 2008) found that the widely observed association of gender with depression became insignificant when controls were included for latent internalizing and externalizing dimensions, arguing that gender is more directly associated with these overall latent dimensions than with depression or any other disorder within these dimensions. In another example, Kessler and colleagues (Kessler, McLaughlin, Green, Gruber, Sampson, et al., 2010) found that the effects of childhood adversities on the onset of individual mental disorders were largely mediated by more direct effects on predispositions for internalizing and externalizing disorders.

One special class of latent variable risk-factor studies uses samples of twins to estimate the effects of genetic factors on comorbidity. These studies suggest that much of the comorbidity between particular pairs of mental disorders in epidemiological samples, as between nicotine dependence and major depression (Lyons, Hitsman, Xian, Panizzon, Jerskey, et al., 2008), can be explained by a latent variable model that assumes the existence of genetic influences. Other studies have shown that decomposition of factor analyses into separate additive genetic and environmental components finds stable internalizing and externalizing factors only for genetic and not environmental influences (Kendler, Aggen, Knudsen, Roysamb, Neale, et al., 2011; Kendler, Prescott, Myers, & Neale, 2003). However, it is important to note that the findings of strong genetic influences on comorbidity are constrained by the assumption of additivity (i.e., no interactions between genetic and environmental effects) and equal environment (i.e., comparability of environmental similarity between identical and nonidentical twins) in the models used to estimate heritability from samples of twins. These assumptions have long been the subject of controversy (Lewontin, 1974). Great care is consequently needed in interpreting these results because of their sensitivity to these assumptions (Molenaar, 2010). An additional important implication, even if we are prepared to accept the results of twin studies, is that the term *genetic* has a much broader meaning than typically appreciated. For example, as noted famously by Lewontin many years ago (Levins & Lewontin, 1985), a genetic effect on tryptophan metabolism has mediating effects through "melanin deposition to skin color to hiring discrimination to lower income." This effect would emerge in a standard twin analysis as documenting strong "heritability for 'economic success'" even if the true driving force behind the association were hiring discrimination based on skin color.

A number of the risk-factor studies described above have treated latent measures of internalizing and externalizing predispositions as independent variables in causal models that predict major depression and other individual disorders. Most of these studies use cross-sectional data and assess comorbidity at a point in time. Although several other studies have used longitudinal data to determine whether the structure of internalizing and externalizing disorders is stable over time (Krueger, Caspi, Moffitt, & Silva, 1998; Vollebergh et al., 2001; Wittchen, Beesdo-Baum, et al., 2009), none has tried to predict onset or persistence of disorders prospectively. Other longitudinal studies have examined temporal progression (Fergusson, Horwood, & Ridder, 2007; Merikangas et al., 2003; Orvaschel, Lewinsohn, & Seeley, 1995; Stein, Fuetsch, Muller, Hofler, Lieb, et al., 2001) or sequencing (Burke, Loeber, Lahey, & Rathouz, 2005; Copeland, Shanahan, Costello, & Angold, 2009; Costello, Mustillo, Erkanli, Keeler, & Angold, 2003; Feehan, McGee, & Williams, 1993; Newman, Moffitt, Caspi, Magdol, Silva, et al., 1996) between earlier and later disorders, documenting strong persistence of disorders over time and predictive associations between some but not other temporally primary and later disorders. Again, though, none of these studies have investigated the extent to which associations of earlier disorders with later disorders were explained by latent internalizing or externalizing variables. For example, Beesdo et al. found that temporally primary social anxiety disorder predicted subsequent onset and persistence of major depression (Beesdo et al., 2007) but did not study whether these associations were due to effects of latent internalizing or externalizing predispositions.

The Dynamic Structure of Comorbidity

Reviews of the literature on developmental psychopathology suggest that analysis of the effects of

latent predispositions to mental disorders on onset and progression of individual disorders could be very useful in identifying modifiable risk pathways (Angold, Costello, & Erkanli, 1999; Jensen, 2003). The confirmatory factor analysis approach that has dominated the literature on latent variables in comorbidity does not allow this kind of investigation. However, a related approach implemented in recent analyses of the World Mental Health (WMH) surveys makes this possible (Kessler, Petukhova, & Zaslavsky, 2011). This new approach begins with the observation that factor analytic studies of comorbidity among recent disorders are made up of two separate pieces: associations involving lifetime disorder risk and associations involving disorder persistence. Factor analysis cannot decompose these two components. However, when data are available on AOO and persistence of multiple disorders, decomposition can be achieved by using survival analysis (Hosmer & Lemeshow, 1999) to carry out separate studies of (1) the associations of temporally primary lifetime disorders with the subsequent first onset of temporally secondary disorders and (2) the associations of lifetime comorbidity with persistence of other disorders. Backward recurrence models can also sometimes be used to study predictors of persistence (Zelen, 2004).

Consider a situation where we are studying comorbidities of major depression with D other disorders with a focus on predictors of first lifetime onset. We would have $D + 1$ survival equations (i.e., one to predict onset of each disorder). There would be D predictors in each equation (i.e., one predictor for prior lifetime occurrence of each other disorder at time t to predict onset of a focal disorder between times t and $t + 1$) and $(D + 1)$ x D coefficients across all the equations (Figure 36.1). The latent variable formulation proposed by the WMH investigators, in comparison, assumes that these coefficients are mediated by latent predispositions to classes of disorders (e.g., internalizing and externalizing disorders) that can change between times t and $t + 1$ (Figure 36.2). As these two models are nested (i.e., the model in Figure 36.2 is a special case of the model in Figure 36.1), it is possible to compare model fit using standard fit indices. It is also possible to modify the model to allow for direct effects of some temporally primary disorders on subsequent onset of some secondary disorders. The model can be used to consider any number of latent variables.

This latent variable model cannot be estimated with the factor analysis approach used in previous studies of the structure of comorbidity because the number of person-years in the survival analysis varies across outcomes. It is also important to note that the model does not assume a factor analytic structure in which the latent variables *cause* the observed disorders and the prediction errors for the observed disorders are conditionally independent. Instead, the model assumes that the observed disorders are the *predictors* of the latent variables. These predictors can be intercorrelated at time t because of joint influences. In this way, the model assumes that the latent variables represent common pathways by which the time t predictors influence multiple outcomes at time $t + 1$. Estimation of coefficients

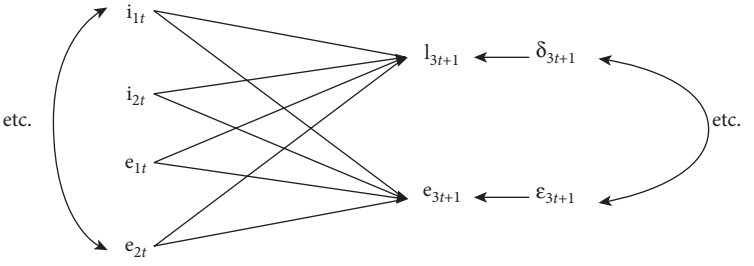

Figure 36.1 Schematic of the multivariate observed variable model.[1]

[1]Only two observed lifetime time t internalizing disorders (e.g., *i1t* represents internalizing disorder 1 at time *t*) and externalizing disorders along with only one observed internalizing and one observed externalizing disorder at time t + 1 are shown to simplify the presentation, but there were much larger numbers of observed lifetime internalizing and externalizing disorders in the actual survival model at each time point. First onset of each of these disorders between times t and $t + 1$ was predicted by prior lifetime history of the other disorders as of time *t*. Estimation was made in a separate survival equation for each outcome disorder, each equation having predictors for prior history of the other disorders. The predictor disorders were treated as time-varying covariates in a discrete-time (person-year) survival framework. Controls were also included for respondent age at interview, sex, person-year, and country. This figure appeared previously in Kessler, R. C., Cox, B. J., Green, J. G., Ormel, J., McLaughlin, K. A., Merikangas, K. R., . . . Zaslavsky, A. M. (2011). The effects of latent variables in the development of comorbidity among common mental disorders. Depression and Anxiety. 28, 32, © Wiley-Liss, Inc. Used with permission.

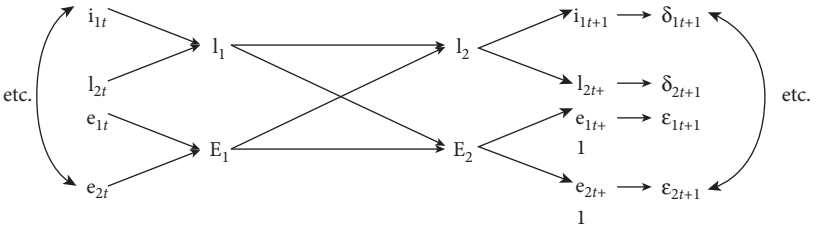

Figure 36.2 Schematic of the multivariate latent variable model.[1]

[1]Only two observed lifetime time t internalizing disorders (e.g., i1t represents internalizing disorder 1 at time t) and externalizing disorders and only three disorders of each set at time t+1 are shown to simplify the presentation, but there were much larger numbers of observed lifetime internalizing and externalizing disorders in the actual survival model. First onset of each of these disorders between times t and t+1 was predicted by latent internalizing or latent externalizing variables at time t+1 in the NCS-2. These time t latent variables, finally, were predicted by lifetime history of observed internalizing or externalizing variables as of time t. As in the earlier observed variable model, the predictor disorders were treated as time-varying covariates in a discrete-time (person-year) survival framework and controls were included for respondent age at interview, sex, person-year, and country.

This figure appeared previously in Kessler, R. C., Cox, B. J., Green, J. G., Ormel, J., McLaughlin, K. A., Merikangas, K. R., . . . Zaslavsky, A. M. (2011). The effects of latent variables in the development of comorbidity among common mental disorders. Depression and Anxiety 28, 33, © Wiley-Liss, Inc. Used with permission.

is complicated by the fact that survival models are involved across a range of outcomes in which first onsets vary from person to person and from year to year. Complex iterative methods described by the WMH investigators are consequently needed to estimate model coefficients. The description of these methods is beyond the scope of this chapter, but we refer interested readers to the exposition by the WMH investigators (Kessler, Ormel, et al., 2011).

This approach was used to study the structure of lifetime comorbidity between major depression and 17 other DSM-IV disorders assessed in the WMH surveys (Kessler, Ormel, et al., 2011). Point-in-time comorbidity among these disorders was found to fit the same two-factor internalizing-externalizing disorders factor model as in earlier factor analysis studies. Major depression had a very strong loading on the internalizing factor. Retrospective AOO reports were then used to estimate a series of 18 survival equations in which first onset of each disorder was predicted by prior lifetime onset of the other 17 disorders along with basic sociodemographic controls. As a result, 98.0% of the 306 (18 x 17) survival coefficients were found to be positive and 95.1% significant in bivariate models. Moreover, 80.0% of the survival coefficients were positive and 43.0% were positive and statistically significant in multivariate models. We also compared two types of associations: within-domain time-lagged associations (i.e., earlier internalizing disorders predicting subsequent first onset of other internalizing disorders or earlier externalizing disorders predicting subsequent first onset of other externalizing disorders) and between-domain associations (i.e., earlier internalizing disorders predicting subsequent first onset of externalizing disorders and earlier externalizing disorders predicting subsequent first onset of internalizing disorders). The former associations (i.e., within-domain) were generally stronger than the latter associations (i.e., between-domain).

A latent variable model was then estimated and found to fit the data much better than the observed variable model. The most important predictors of the latent internalizing dimension were specific phobia, followed by obsessive compulsive disorder and other phobias. Major depression was intermediate in importance as a predictor of the latent internalizing dimension. The most important predictors of the latent externalizing dimension, in comparison, were hyperactivity disorder (the subset of attention-deficit/hyperactivity disorder cases with six or more hyperactivity and/or impulsivity symptoms) and oppositional-defiant disorder.

Controls for the latent variables explained the vast majority of the originally significant time-lagged associations among observed disorders. Indeed, there were only 13 residual pair-wise time-lagged associations between observed disorders that remained significant after controlling the latent dimensions. And only one of these 13 involved major depression: a positive association between temporally primary major depression and the subsequent onset of generalized anxiety disorder (GAD). Importantly, there was no significant reciprocal association between temporally primary GAD and subsequent major depression. Disaggregation found that the significant association of depression with subsequent GAD, while found both for childhood-onset and adolescent-onset cases, did not persist in predicting adult-onset cases of GAD.

At the level of the latent dimension, significantly stronger ORs were found for within-domain than between-domain time-lagged associations even though all four of these ORs were statistically significant. Specifically, the within-domain ORs were 1.6 for internalizing and 1.4 for externalizing compared with between-domain ORs of 1.3 for time *t* internalizing predicting time *t* + 1 externalizing and 1.1 for time *t* externalizing predicting time *t* + 1 internalizing. The consistently significant cross-lagged associations led to significant comorbidities of major depression with externalizing disorders. The good fit of the latent variable model suggests that common causal pathways account for most comorbidity among the disorders considered.

Lifetime Comorbidity and Persistence-Severity of Disorders

The analyses described in the previous subsection focused on predicting lifetime onset of secondary comorbid disorders. Another issue of importance is disorder persistence. It has long been known that lifetime comorbidity predicts persistence of a wide range of comorbid mental disorders (Hagnell & Grasbeck, 1990; Murphy, 1990). In a national epidemiological survey of the United States, for example, the association (OR) of lifetime comorbidity (i.e., lifetime prevalence of any other DSM disorder) with current major depression among respondents with a lifetime history of major depression was 2.3 even after controlling for AOO and time-since-onset of depression (Kessler, 1995). Other studies have documented that lifetime comorbidities of major depression with both panic disorder (Roy-Byrne, Stang, Wittchen, Üstün, Walters, et al., 2000) and social phobia (Wittchen & Fehm, 2001) predict increased persistence of both disorders in each of these pairs. An exception is that lifetime GAD-depression comorbidity seems to predict only persistence of depression, not persistence of GAD (Kessler, Gruber, Hettema, Hwang, Sampson, et al., 2008).

Parallel research has shown that both lifetime and recent comorbidities among mental disorders are associated with the severity of the component disorders (Alonso, Vilagut, Chatterji, Heeringa, Schoenbaum, et al., 2011; Gadermann, Alonso, Vilagut, Zaslavsky, & Kessler, 2012; Ormel, Petukhova, Chatterji, Aguilar-Gaxiola, Alonso, et al., 2008). In a national epidemiological survey of the United States, for example, the proportion of respondents with 12-month major depression who met criteria established by the U.S. Substance Abuse and Mental Health Services Administration for a *serious mental illness* (SMI) (Substance Abuse and Mental Health Services Administration, 1993) was twice as high among cases with 12-month comorbidity (45.6%) and 1.5 times as high among cases with lifetime (but not 12-month) comorbidity (31.6%) as among cases without lifetime comorbidity (21.0%) (Kessler, 1997).

However, virtually all research on the association between comorbidity and disorder persistence-severity has focused either on specific disorder pairs, such as comorbid panic-depression (Roy-Byrne et al., 2000) or GAD-depression (Wittchen, Carter, Pfister, Montgomery, & Kessler, 2000), or comorbidity between major depression and any other common mental disorder (Kessler, 1995, 1997). As a result, we do not know whether the significant associations of major depression with persistence-severity of comorbid disorders are due to depression itself or to other comorbid disorders. Future research along the lines of the WMH analyses predicting first lifetime onset of secondary comorbid disorders is needed to study these specificities.

Comorbidities of Major Depression with Physical Disorders

Basic Patterns of Comorbidity

It is now well established that major depressive disorder (MDD) is significantly associated with a wide variety of chronic physical disorders, including arthritis, asthma, cancer, cardiovascular disease, diabetes, hypertension, chronic respiratory disorders, and a variety of chronic pain conditions (Anderson, Freedland, Clouse, & Lustman, 2001; Buist-Bouwman, de Graaf, Vollebergh, & Ormel, 2005; Chapman, Perry, & Strine, 2005; Derogatis, Morrow, Fetting, Penman, Piasetsky, et al., 1983; Dew, 1998; McWilliams, Cox, & Enns, 2003; Nemeroff, Musselman, & Evans, 1998; Ortega, Feldman, Canino, Steinman, & Alegria, 2006; Wells, Golding, & Burnam, 1989). Although most of the data documenting these associations comes from clinical samples in the United States, similar data also exist from community epidemiological surveys carried out throughout the world (Scott, Bruffaerts, Tsang, Ormel, Alonso, et al., 2007; Von Korff, Scott, & Gureje, 2009). These associations have considerable individual and public health significance and can be thought of as representing costs of depression in at least two ways. First, to the extent that depression is a causal risk factor, it leads to an increased prevalence of these

physical disorders, with all their associated financial costs, impairments, and increased mortality risk. Evidence about depression as a cause of these physical disorders is spotty, although we know from meta-analyses of longitudinal studies that MDD is a consistent predictor of the subsequent first onset of coronary artery disease (Van der Kooy, van Hout, Marwijk, Marten, Stehouwer, et al., 2007; Wulsin & Singal, 2003), stroke (Ohira, Iso, Satoh, Sankai, Tanigawa, et al., 2001), diabetes (Carnethon, Kinder, Fair, Stafford, & Fortmann, 2003), heart attacks (Pratt, Ford, Crum, Armenian, Gallo, et al., 1996; Scherrer, Virgo, Zeringue, Bucholz, Jacob, et al., 2009), and certain types of cancer (Gross, Gallo, & Eaton, 2010). Comorbid depression is also often associated with a worse course of these physical disorders (Gillen, Tennen, McKee, Gernert-Dott, & Affleck, 2001; Mancuso, Rincon, McCulloch, & Charlson, 2001; Peyrot & Rubin, 1997).

It should not be surprising in light of the facts in the previous paragraph that MDD is associated with a significantly elevated risk of early death (Carney, Freedland, Miller, & Jaffe, 2002; Cuijpers & Schoevers, 2004; Wulsin, Vaillant, & Wells, 1999). This is true partly because people with MDD have a high suicide risk (Bostwick & Pankratz, 2000; Moller, 2003; Rihmer, 2007) but also because depression is associated with an elevated risk of the many types of physical disorders noted above. Depression is also associated with elevated mortality risk among people with certain kinds of disorders as part of a larger pattern of associations of depression with disorder severity. There has been particular interest in depression as a risk factor for cardiovascular mortality due to heart attack and stroke among people with cardiovascular disease (CVD) (Barth, Schumacher, & Herrmann-Lingen, 2004; Gump, Matthews, Eberly, & Chang, 2005; Lesperance, Frasure-Smith, Talajic, & Bourassa, 2002; van Melle, de Jonge, Spijkerman, Tijssen, Ormel, et al., 2004). Indeed, a number of interventions have been developed to detect and treat depression among people with CVD in an effort to prolong life, although the results of these studies have so far been only modest (Thombs, de Jonge, Coyne, Whooley, Frasure-Smith, et al., 2008).

Potential Causal Mechanisms

A number of biologically plausible mechanisms have been proposed to explain the prospective associations of depression with chronic physical disorders (Carney, Freedland, Miller, & Jaffe, 2002; Cohen & Rodriquez, 1995; Cuijpers & Schoevers, 2004; Katon & Ciechanowski, 2002; Stapelberg, Neumann, Shum, McConnell, & Hamilton-Craig, 2011). These include a variety of poor health behaviors known to be linked to depression, such as elevated rates of smoking and drinking (Davis, Uezato, Newell, & Frazier, 2008), obesity (Cizza, 2011), low compliance with treatment regimens (Schlenk, Dunbar-Jacob, & Engberg, 2004; Ziegelstein, Fauerbach, Stevens, Romanelli, Richter, et al., 2000), and a variety of biological dysregulations, such as hypothalamic-pituitary-adrenal hyperactivity and impaired immune function (Kiecolt-Glaser & Glaser, 2002). Based on these observations, there is good reason to believe that depression might be a causal risk factor for at least some chronic physical disorders. Second, even if depression is more a consequence than a cause of chronic physical disorders, as it appears to be for some disorders based on stronger prospective associations of depression onset subsequent to, rather than before, onset of the physical disorder, comorbid depression is often associated with a worse course of the physical disorder (Gillen, Tennen, McKee, Gernert-Dott, & Affleck, 2001; Mancuso, Rincon, McCulloch, & Charlson, 2001; Peyrot & Rubin, 1997). A number of reasons could be involved here, but one of the most consistently documented is that depression is often associated with nonadherence to treatment regimens (Breitbart, Rosenfeld, Pessin, Kaim, Funesti-Esch, et al., 2000; Cluley & Cochrane, 2001; Ziegelstein et al., 2000).

An obvious possibility raised by these results is that interventions could be developed to detect and treat comorbid MDD among patients with chronic physical disorders in an effort to reduce the persistence-severity of these physical disorders. A number of controlled interventions of this type have been implemented among patients with various kinds of cardiovascular disorders. The effects of these interventions on persistence-severity of cardiovascular disorders have been disappointingly weak (Thombs et al., 2008). This is true despite the fact that some antidepressant medications have been found to have direct biological effects in improving cardiovascular disease (Paraskevaidis, Parissis, Fountoulaki, Filippatos, & Kremastinos, 2006). Based on these disappointing results, recent interventions designed to detect and treat depression among patients with chronic physical disorders have focused on the quality-of-life effects of ameliorating the distress caused by the physical disorders rather than on any potential effects on the course

of the physical disorders (Meijer, Roseman, Milette, Coyne, Stefanek, et al., 2011), although there is still some suggestion that the detection and treatment of comorbid MDD might have positive effects on clinical outcomes for other chronic physical disorders (Fritzsche, Clamor, & von Leupoldt, 2011).

An obvious area of future research suggested by our earlier discussion of comorbidity between MDD and other mental disorders is that studies of comorbidity between MDD and chronic physical disorders should be expanded to consider a wider range of mental disorders. We do not know, for example, something as simple as whether anxious depression and nonanxious depression are equally associated with chronic physical disorders or whether the associations of MDD with physical disorders could be partly explained by introducing controls for other comorbid mental disorders. It is quite possible that information along these lines would have implications for targeting and revising the content of clinical interventions to treat comorbid mental disorders that would yield more powerful evidence than currently exists for ameliorative effects of such interventions on the persistence and course of comorbid physical disorders.

In light of the limited evidence suggesting that the detection and treatment of comorbid MDD leads to significant improvements in the persistence and severity of chronic physical disorders, increasing attention has been given to cases of depression that might be consequences of physical disorders. One such type that has been the subject of considerable interest is *vascular depression* (Naarding & Beekman, 2011); that is, depression caused by vascular brain disease. Krishnan and colleagues (Krishnan, Hays, & Blazer, 1997) were the first modern researchers to propose the existence of vascular depression. They did this based on evidence of vascular lesions on MRIs among some patients with late-onset depression. These researchers suggested that vascular depression is associated with a symptom profile featuring pronounced cognitive impairment, psychomotor retardation, and anhedonia. Subsequent clinical studies have shown that cases of depression occurring for the first time after vascular events (as in the wake of a diagnosis of heart disease or after a stroke or heart attack) have a particularly persistent and severe course (Naarding & Beekman, 2011). However, epidemiological data have been mixed about the existence of a symptom profile thought to typify vascular depression in the general population (Naarding, Tiemeier, Breteler, Schoevers, Jonker, et al., 2007; Naarding, Veereschild, Bremmer, Deeg, & Beekman, 2009). A recent study, though, found that subthreshold vascular disease is associated with higher levels of somatic than cognitive depression symptom scores (Bus, Marijnissen, Holewijn, Franke, Purandare, et al., 2011), raising the possibility of bias in the assessment of MDD among patients with cardiovascular disorders. This is something clearly requiring further research.

Age Differences in Comorbidity of Major Depression with Physical Disorders

The possible existence of a vascular type of MDD raises the issue of age differences in comorbidity between depression and chronic physical disorders. This is a complex area of investigation in light of the fact that while many chronic physical disorders increase with age, the opposite seems to be true of MDD. That is, community epidemiological surveys in developed countries consistently find that current prevalence of MDD decreases with age and is especially low among the elderly (Jorm, 2000; Trollor, Anderson, Sachdev, Brodaty, & Andrews, 2007). A number of methodological explanations have been proposed for this finding, suggesting that age-related differentials in mortality, selection out of the household population, willingness to participate in surveys, and willingness to admit psychiatric problems lead to downward bias in prevalence estimates among the elderly (Schoevers et al., 2009; Snowdon, 1997). However, evidence for these methodological interpretations is weak (Ernst & Angst, 1995), leading some commentators to conclude that the prevalence of depression is genuinely low among the elderly (Blazer & Hybels, 2005).

Among the possible methodological explanations for the declining prevalence of MDD with age is that depression might be increasingly underestimated with increasing age because the symptoms of depression are confused with the symptoms of physical disorders (Drayer, Mulsant, Lenze, Rollman, Dew, et al., 2005). Additional complicating factors, of course, are that some somatic disorders that increase with age can induce depression (Bremmer et al., 2008; Salaycik, Kelly-Hayes, Beiser, Nguyen, Brady, et al., 2007), while late-life depression can increase risk of some physical disorders (Bremmer, Deeg, Beekman, Penninx, Lips, et al., 2007; Petronijevic, Petronijevic, Ivkovic, Stefanovic, Radonjic, et al., 2008). Taken together, these considerations make it quite clear that age is a variable of great importance in understanding comorbidities of MDD with chronic physical disorders.

In an effort to shed light on the importance of age in this regard, a number of recent community epidemiological studies examined variation in the comorbidities of MDD with chronic physical disorders over the life course. The largest of these studies were carried out in the cross-national WMH Surveys (Kessler, Birnbaum, Bromet, et al., 2010; Scott, Von Korff, Alonso, Angermeyer, Bromet, et al., 2008), with the most comprehensive report based on interviews with nearly 90,000 respondents across 18 different countries (Kessler, Birnbaum, Shahly, et al., 2010). Recent DSM-IV MDD was defined in these analyses without organic exclusions to facilitate investigation of comorbidity, while self-report chronic condition checklists were used to assess physical disorders. Such checklists are widely used in epidemiological studies and yield more accurate reports than open-ended questions (Knight, Stewart-Brown, & Fletcher, 2001). Good concordance has been documented between condition reports based on such checklists and medical records (Baker, Stabile, & Deri, 2004; Edwards, Winn, Kurlantzick, Sheridan, Berk, et al., 1994; Revicki, Rentz, Dubois, Kahrilas, Stanghellini, et al., 2004).

Consistent with many previous studies (Blazer, Hughes, & George, 1987; Kennedy, Kelman, & Thomas, 1990), the WMH data showed that recent prevalence of MDD decreased with age while recent prevalence of most chronic physical disorders increased with age. Age was also positively associated with *longer* duration but *lower* role impairment of recent depressive episodes across the full range of WMH surveys. The age difference in role impairment is consistent with a number of independent studies (Ernst & Angst, 1995; Koenig, Meador, Shelp, Goli, Cohen, et al., 1991). One plausible interpretation of this finding is that role demands decrease with age. However, this interpretation does not explain the finding that recent depression symptom severity was also found to decrease significantly in some WMH countries. The latter finding raises the possibility suggested by several commentators that depression subtypes change with age and that the subtypes more typical of older people are less severe and impairing than those more typical of younger people (Newmann, Klein, Jensen, & Essex, 1996; Sneed, Rindskopf, Steffens, Krishnan, & Roose, 2008). No attempt was made in the WMH analyses to examine depressive symptom profiles by age to investigate this interpretation. However, given the large size and wide geographic distribution of the WMH database, this would be a potentially valuable future extension of these analyses.

Comorbidities of current MDD with current physical disorders generally *decreased* with age in the WMH data, while comorbidities of MDD with other DSM-IV mental disorders generally *increased* with age. The most plausible interpretation of the generally increasing age-related ORs with other mental disorders is one noted earlier in this chapter in the discussion of comorbidities of MDD with other mental disorders: that comorbid cases have a more persistent course than pure cases. This could also be implicated in the longer duration of depressive episodes among the elderly. The fact that the role impairment associated with depression was found to be lowest among the elderly is all the more striking in light of this higher comorbidity of MDD with other mental disorders among elderly cases.

The generally decreasing age-related ORs of MDD with physical disorders are more interpretable because the age patterns in prevalence were different for major depressive episodes (MDEs) (decreasing prevalence with age) compared with most physical disorders (increasing prevalence with age). In a situation of this sort, it is likely that the decreasing ORs are at least partially attributable to a decrease in the causal effects of physical disorders on depression. Whether or not causal effects of depression on comorbid physical disorders also decrease with age is difficult to say because the implications of such a decrease on the prevalence of physical disorders would be negligible in light of the much lower prevalence of MDD than chronic physical disorders among the elderly. In either case, though, the existence of these patterns argues against the suggestion that the low prevalence of depression among the elderly is due to increased confounding of depression symptoms with symptoms of chronic physical disorders.

Future Directions

Based on the results reviewed above regarding comorbidities of MDD with other mental disorders, it appears that the common pathways defined by latent internalizing and externalizing dimensions (as well as by more refined latent dimensions that might be found in future studies) would be a useful focus of future research on the development of comorbidity between MDD and other mental disorders. Parallel studies are also needed on the associations of comorbidity with disorder persistence and severity. It is important to note, though, that the WMH analyses were based on cross-sectional data that used retrospective AOO reports to infer temporal sequencing. Because of this serious limitation,

WMH results need to be replicated and confirmed prospectively before they are considered definitive. An effort to do this in a large 10-year multiwave prospective epidemiological survey in Germany is currently underway (Wittchen, Perkonigg, Lachner, & Nelson, 1998).

Making the provisional assumption that these WMH results are accurate, it is important to note that MDD was found to be a much less powerful predictor of the subsequent onset of secondary disorders in the dynamic latent liability framework than in more conventional bivariate models. This is true because MDD was found to be significantly associated with a wide range of other common mental disorders that accounted for substantial components of the bivariate associations between MDD and later disorders.

MDD was temporally secondary to a majority of the comorbid disorders that explained the bivariate associations of MDD with later disorders. This was especially true for attention-deficit/hyperactivity disorder (ADHD), intermittent explosive disorder (IED), oppositional-defiant disorder (ODD), separation anxiety disorder (SAD), social phobia, and specific phobia. All of these disorders are consistently found in epidemiological studies to have much earlier AOO distributions than MDD (de Girolamo, Dagani, Purcell, Cocchi, & McGorry, 2012; Kessler et al., 2007; McGorry, Purcell, Goldstone, & Amminger, 2011). ADHD and SAD have median AOO in early to middle childhood. IED, ODD, and social phobia have median AOO in middle to late chilhood and early adolescence. Major depression, in comparison, has median AOO in the early to middle twenties and also has a much wider AOO range than the temporally primary disorders. By virtue of begininng at earlier ages, the reduction in strength of associations between MDD and later disorders can be said to be partially *explained* by these earlier disorders. However, the word *explained* is used here in the statistical sense rather than the causal sense. It might be that these earlier disorders are causes of both depression and later comorbid disorders. Or these earlier disorders might be risk markers for some other as yet undetermined underlying common causes of depression and later disorders (Kraemer et al., 1997). We have no definitive way to adjudicate between these possibilities with nonexperimental epidemiological data. However, the approach used to analyze the WMH data could be expanded to help pinpoint multivariate profiles of earlier disorders that predict onset of both MDD and later comorbid disorders for purposes of targeting experimental interventions aimed at timely treatment of these earlier disorders. These interventions could provide definitive data on the causal role of temporally primary disorders in accounting for the associations of MDD with subsequent mental disorders.

While the comorbid disorders mentioned in the previous paragraph typically have onset prior to MDD, three other comorbid disorders more typically have onsets closer in time to MDD. These three are GAD, panic disorder, and posttraumatic stress disorder (PTSD). These are the internalizing disorders most strongly comorbid with MDD (Kessler, 1995, 1997; Kessler, Ormel, et al., 2011). Two of the three, GAD and panic disorder, have AOO distributions very similar to depression, with median AOO in the the early to middle twenties and a very wide AOO range. PTSD is somewhat different in having a more variable onset distribution. This is presumably because the traumatic experiences that lead to PTSD are often random in their times of occurrence. With one notable exception, MDD is as strong a predictor of the onset, persistence, and severity of these three disorders, as they are of the onset, persistence, and severity of MDD. The exception, noted above, involves GAD: that major depression predicts subsequent onset of GAD more strongly than GAD predicts subsequent onset of MDD (Kessler, Ormel, et al., 2011), while comorbid GAD predicts persistence and severity of MDD more strongly than comorbid depression predicts persistence and severity of GAD (Kessler et al., 2008).

The strong reciprocal comorbidities of MDD with these three disorders raise the possibility of two potentially important types of interventions aimed at secondary prevention. The first type would be of interventions designed to prevent the onset of these three other disorders among patients with recent onsets of MDD. Interventions of this first type might be useful in reducing the persistence of MDD. The second type would be interventions designed to treat current episodes of these three disorders among patients with comorbid MDD. Interventions of this second type might be helpful in reducing the severity of episodes of MDD.

The results reviewed here on comorbidities of MDD with chronic physical disorders are intriguing but raise many questions for future research. The WMH data are quite clear in suggesting that physical disorders, which increase in prevalence with age, have decreasing effects on depression with age in light of the inverse association between age and

MDD and, even more strikingly, the inverse association between age and the ORs between chronic physical disorders and MDD. Yet the WMH data shed no light on why these age-related differences in comorbidity might occur. One possibility proposed in the literature is that elderly people are more accepting than younger people of the inevitability of physical illness, resulting in the otherwise adverse psychological effects of physical disorders being buffered (Ernst & Angst, 1995). A related suggestion is that elderly people are "immunized" from the negative psychological effects of adversity by prior life experience (Henderson, Montgomery, & Williams, 1972). Although we are aware of no direct test of these hypotheses, elderly people have been shown to be more likely than younger people to cope with adversity by using strategies that accept and adapt rather than try to change their situations (Diehl, Coyle, & Labouvie-Vief, 1996) and that disengage from stressful situations in ways that reduce adverse emotional effects (Charles & Carstensen, 2008). Other research has shown similar age differences in coping with physical illness (Felton & Revenson, 1987) but has not investigated whether these differences lead to reductions in the causal effects of physical disorders on depression. More focused future investigation of these buffering effects could be important in shedding light on positive patterns of response to the increasing physical infirmity of advanced age. Another possibility is that elderly people might have reduced capacity to register or express mood states owing to autonomic, neuroendocrine, or cognitive dysfunction leading to a reduced prevalence of mood disorders in old age (McEwen, 2007).

Author Notes

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CHAPTER

37 Epilogue

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Abstract

The authors of the chapters in this volume have covered nearly every feature of depression comorbidity with other psychiatric disorders, chronic health conditions, and disturbed close relationships. Treatment implications are addressed both in chapters on individual disorders as well as comprehensively in separate chapters. This volume concludes with the "big picture" provided by Ronald Kessler and his colleagues. Several themes emerge. Depression comorbidity is pervasive. It touches to one degree or another almost every identifiable psychiatric condition, chronic health condition, and disturbed close relationship. There are numerous potential explanations for this pervasive comorbidity that depend in part on the comorbid disorder. Depression comorbidity is associated with greater disease burden, resistance to treatment, increased primary disease morbidity, and mortality relative to cases in which comorbid depression is not present. Although depression comorbidity is common across psychiatric disorders, it is especially common among the anxiety disorders, raising questions as whether these disorders are really distinct. The assessment and treatment of comorbid disorders is complicated and often requires interdisciplinary collaboration. Although great strides have been made in the study of depression comorbidity, there is much left to be learned, so that we will be able to provide the most effective possible care to our patients who suffer from comorbid depression.

Key Words: depression comorbidity, chronic health conditions, disease burden, assessment and treatment, effective care

According to the Merriam-Webster online dictionary, an epilogue is a "concluding section that rounds out the design of a literary work." In many novels, epilogues seem to tie up loose ends and enlighten the reader as to the fate of important characters. In one sense, the chapters in this book leave very little room for a conventional epilogue. They cover nearly the entire universe of depression comorbidity, and the concluding chapter, by Ronald Kessler and his colleagues, provides what we call "the big picture," which ties together issues arising from depression comorbidity with other psychiatric disorders and chronic health conditions. What was not known to the authors (for the most part) was the ultimate fate of the revisions to the DSM. DSM-5 (American Psychiatric Association, 2013) was published after the manuscripts for these chapters were safely in the hands of the publisher. Nevertheless, perhaps the best way to characterize the changes from DSM-IV-TR to DSM-5 would be to say, "The more things change, the more they stay the same." Very little changed in the DSM that would have a bearing on our authors' analyses of the problem of depression comorbidity.

Several themes emerged that bear comment in this concluding chapter. First, comorbidity is pervasive. Depressive symptoms and syndromal depression are very common in other psychiatric disorders, chronic health conditions, and disturbed close relationships. Explanations for this comorbidity

are varied and include shared liability (e.g., depression and anxiety disorders), overlapping symptoms (e.g., depression and anxiety disorders, most chronic health conditions), common biological factors reflected in immune function and the activity of the hypothalamic-pituitary-adrenal axis (e.g., depression and coronary heart disease), depression caused by another psychiatric disorder or chronic health condition (e.g., depression and social anxiety disorder; depression and cancer), and depression brought on by medical treatments (e.g., depression and medications for multiple sclerosis [MS]). Another theme is that depression is an extremely common complication of the anxiety disorders, so much so that questions have been raised as to whether depression and these disorders (e.g., generalized anxiety disorder [GAD] and posttraumatic stress disorder [PTSD]) are really distinct. A third theme is that depressive comorbidity is associated with a greater disease burden (morbidity and mortality) and poorer course and treatment response for most psychiatric disorders, chronic health conditions, and disturbed personal relationships. Finally, the assessment and treatment of comorbid conditions can be complex and require the clinician to exercise considerable flexibility and imagination. The remainder of this epilogue briefly addresses each of these issues.

Pervasiveness of Comorbidity

Comorbidity is ubiquitous, particularly comorbidity of depression with other psychiatric disorders, chronic health conditions, and distressed close relationships. The authors of this volume's chapters have captured the breadth of comorbidity as it relates to depression. Nevertheless, as Widiger and Gore (Chapter 2) point out, comorbidity is not just a problem for depression; comorbidity issues saturate the recent editions of the DSM. For example, in the DSM-5 manual index (American Psychiatric Association, 2013) comorbidity is listed 45 times just through the letter E.

The principal focus of this volume is the way in which depression may complicate the diagnosis and treatment of other psychiatric disorders and health conditions as well as distressed close relationships. Of course comorbidity is a two-way street. Widiger and Gore, and in one way or another all of the authors, make it clear that when one is confronted with a patient experiencing major depression, there is a good likelihood that he or she will carry additional diagnoses, will have concomitant chronic health problems, and may be embedded in dysfunctional close relationships. For example, Widiger and Gore point to the several waves of the National Comorbidity Study (Kessler, Berglund, et al., 2003), in which, among individuals with a major depressive disorder, 72% had a comorbid condition, the most frequent being anxiety disorder (59%), substance use disorder (24%), and an impulse control disorder (30%). Among adolescents with a diagnosis who were surveyed in a later wave, about 40% had a comorbid psychiatric disorder, with mood disorder being the most likely to co-occur with other disorders (Merikangas et al., 2010).

Depression is a significant complication for persons with chronic health conditions. Chapters 18 through 27 take on this issue with respect to chronic health conditions including coronary heart disease (CHD), cancer, pain, obesity, sleep disorders, multiple sclerosis (MS), HIV/AIDS, kidney disease, dementia, diabetes, fibromyalgia, and rheumatoid arthritis. What is striking in these chapters is that similar issues arise for each of the chronic health conditions. In almost every case, rates of depression are high relative to the general population. For example, point prevalence rates of depression in multiple sclerosis (Chapter 23) range from 14% to 25.7%. For coronary heart disease (Chapter 18) the range is 14% to 47%, and for HIV/AIDS (Chapter 24), it is 36%. Rates of depression for other chronic health conditions are similarly high. The quality of the studies that provide these estimates is quite variable, but the evidence converges to the conclusion that depression is very common in individuals with chronic health conditions.

What is it about depression that makes it so likely to occur with other disorders? The first several chapters of this volume addressed this question and provide important perspectives on how one might view comorbidity and why depression might be such a common partner in psychiatric comorbidity.

Causes of Comorbidity

SHARED LIABILITY

The challenges of comorbidity may be best highlighted in the context of depression but are by no means limited to depression. Perhaps the first challenge is to answer the question, "What is comorbidity or how is it defined?" How can it be modeled? Markon (Chapter 3) points to two general models of comorbidity—the exogenous co-occurrence model that focuses on the co-occurrence of two or more conditions (e.g., depression and cancer) and the effects of this co-occurrence on other variables,

such as social impairment or treatment response. A second paradigm is the endogenous covariance model, which focuses on the association between two or more conditions in a group of individuals and attempts to explain the causes of the covariance. For example, what is the common underlying cause (or liability) that explains the frequent comorbidity of depression and anxiety disorders? He and others suggest that there is probably a common genetic liability that explains their frequent co-occurrence. The exogenous model might best apply to the comorbidity of depression and chronic health conditions, which presumably have distinct etiologies. However, Markon argues that even in these cases depression may in fact affect the chronic condition, in making it worse, or the chronic health condition may lead to the onset of depression, suggesting that an endogenous model might be a more appropriate representation of this type of comorbidity. Markon points to the example of diabetes and depression (Chapter 27), but another classic case is that of depression and cardiovascular disease (Chapter 18). Nevertheless, endogenous models have generally been applied to the comorbidity among psychiatric disorders rather than between psychiatric disorders and chronic medical conditions. Markon's chapter provides support for an endogenous model of comorbidity that accounts for the common co-occurrence of depression and anxiety disorders—the link being a basic liability to internalizing symptoms.

This theme is elaborated by Watson and Stasik (Chapter 4) in their chapter on the quadripartite model of depression and anxiety. The quadripartite model has two dimensions for symptoms of depression and anxiety: "high" versus "low" distress symptoms with "greater" or "more limited" specificity to distinguish depression from anxiety disorders. Focusing specifically at the symptom level, they report on a series of studies showing that several of the DSM symptoms of depression are not distinct from one another but in aggregate show good specificity with respect to anxiety disorders. For example, depressed mood, loss of interest, psychomotor retardation, feelings of worthlessness/guilt, and cognitive problems were all highly interrelated and defined a common factor (dysphoria). Nevertheless this factor, which reflects high distress, shows a clearly stronger association with depression than with the anxiety disorders (GAD, PTSD, social phobia, agoraphobia, obsessive compulsive disorder [OCD], specific phobia). Other symptoms including lassitude, the absence of a sense well-being, and suicidality showed a similar pattern. However, some symptoms—including insomnia, appetite loss, and appetite gain—showed very little specificity to depression; hence, in the ordinary course of clinical work, they are not very useful in distinguishing depression from anxiety disorders. Work of this sort did not have much impact on the DSM-5, which acknowledges the comorbidity of anxiety and depression at the syndromal level but does not address it at the symptom level.

OVERLAPPING SYMPTOMS

The problem of overlapping symptoms between depression and other disorders is an acute one. While, for example, symptoms of depression, PTSD, and GAD overlap a great deal, there is also considerable overlap of depression symptoms with symptoms of many chronic health conditions. For example, DSM depression symptoms—such as sleep and appetite disturbance, fatigue/low energy, psychomotor slowness, and difficulty concentrating—are common to CHD, kidney disease, MS, AIDS, and cancer among other chronic health conditions. These symptoms, along with one of the gateway depression symptoms—depressed mood or anhedonia—would fulfill the symptom criteria for depression. Of course given the debilitating effects of many of these chronic health conditions, individuals commonly experience loss of pleasure in their usual activities (anhedonia). As a consequence, the full syndrome of depression could be manifest simply as part of the symptom expression of a chronic health condition. We would traditionally view these expressions of depression as "secondary" to the primary chronic health condition, but that may be a distinction without importance given the extra disease burden associated with comorbid depression.

Various approaches have been taken to address the overlap of depression and the symptoms of chronic health conditions. One approach has been to focus primarily on symptoms that would seem to distinguish depressed from nondepressed individuals with chronic health conditions. For example, in MS, symptoms such as pessimism, guilt, disappointment, sadness, and sense of failure have been shown to be more common in depressed MS patients than nondepressed MS patients. In other cases, clinicians simply evaluate depression symptoms at face value without trying to separate them on the basis of whether they are attributable to depression or a chronic health condition. Because there is no true external validation for a diagnosis of depression beyond the array of symptoms specified in the

DSM, there is no completely satisfactory way of allocating symptoms to depression, to the disorder, or to the treatment (i.e., side effect such as fatigue). Nevertheless, whether symptoms are due to "depression" or not, the greater the number of depressive symptoms and the greater the severity of the symptoms, the more the patient suffers (i.e., from an increased disease burden). The disability associated with this suffering can be addressed through careful selection of antidepressant treatments.

COMMON BIOLOGICAL FACTORS AND CAUSAL DIRECTION

Several of the chapters point to the ongoing debate about whether depression can cause a chronic health condition such as coronary heart disease. Suls and Davidson (Chapter 18) point out that depression confers a twofold risk for cardiac disease incidence and disease progress. They argue that depression can affect heart disease through its impact on immune activity, endothelial function, sympathetic nervous system (SNS) and HPA activity, and medical adherence. They also acknowledge that unknown third variables may be responsible for the association. Despite the evidence that depression may play a role in the onset of heart disease, there is little evidence that the treatment of depression in the context of cardiac disease influences cardiac-related mortality. Like the case for heart disease, common biological factors also would seem to operate in other depression-chronic health condition comorbidities such as pain, sleep disorders, MS, obesity, and dementia. Of course the same issues regarding common biological factors apply to the comorbidity between depression and other psychiatric disorders, particularly the anxiety disorders. A common theme among all of these chapters is the need for new research on the underlying or mediating mechanisms that link depression and other disabling conditions. It is likely that this research will need to be longitudinal, following large population samples probably from an early age in order to adequately test competing causal models and determine direction of causality between depression and other disorders.

DEPRESSION AND SIDE EFFECTS OF INTERVENTION

Most interventions have effects that go beyond what is planned therapeutically. Treatments for serious medical conditions such as cancer, multiple sclerosis, and kidney disease often have side effects that are very unpleasant. In addition to mimicking symptoms of depression, these side effects can simply make the patient feel unwell or limit the patient's ability to function, also diminish sources of pleasure over periods ranging from days to weeks or months or even an entire lifetime (e.g., dialysis for end-stage renal disease). Some of these side effects can be managed medically but others cannot. Interventions aimed at helping patients manage depression associated with treatment and the limitations that medical treatments impose on patients are critical and should be the subject of further research. Additionally, a number of authors have pointed to the challenges of using conventional depression treatments with chronically ill patients because in some cases the depression intervention (usually pharmacotherapy) makes the health condition worse. In the case of psychotherapy, patients may be too unwell to avail themselves of treatment. Research on new approaches to treatment (e.g., home-based treatments) is clearly needed.

The Anxiety Disorders

Four chapters in this volume directly address many issues in the comorbidity of depression and the anxiety disorders. Mineka and her colleagues (Chapter 9) take on the issue of the extensive comorbidity of depression and GAD. They argue that despite the high degree of comorbidity between the two disorders and the recommendations of some researchers, the two disorders should be considered as separate. They identify several points of distinction, including the fact that depression is comorbid to a high degree with the other anxiety disorders, including PTSD, panic disorder, and social phobia. These observations suggest that the problem of comorbidity is not limited to generalized anxiety disorder alone among the anxiety disorders. They go on to argue that the high degree of comorbidity appears to be due in large part to the common genetic underpinning of the two disorders based on twin studies and that differences in environmental/life experiences may determine who goes on to experience one disorder or another or both. A recurring theme in this volume, highlighted by Mineka and her colleagues, is that comorbid depression and GAD carries a heavy burden of disability, which is greater than that of either disorder alone.

PTSD (Chapter 7) is unique in the requirement that some specific event must be identifiable that brings on the symptoms. Of course it is very common for life events to bring on depressive episodes. Traumatic events (PTSD) and loss events (depression) often overlap. Therefore it is not surprising that as in the case of GAD and depression, PTSD

and depression are highly comorbid. Moreover, depression and PTSD appear to increase the risk for each other. Again, similar to the case for depression and GAD, comorbid PTSD and depression impose a greater disability burden on patients than either disorder alone. Finally, as in GAD and depression, there is good evidence of a substantial genetic correlation between the two disorders and a much more modest environmental correlation. Risk factors are similar as well. Najavits and Capezza (Chapter 7) indicate that these similarities have led many researchers to suggest that perhaps comorbid depression and PTSD represent a specific posttraumatic event response and should be considered one disorder separate from PTSD or depression. This is an important question that awaits further research.

Social anxiety disorder (SAD) and depression (Chapter 8) share high negative affect and low positive affect, a characteristic that may in part account for their high degree of comorbidity. Like the other anxiety disorders, SAD would seem to share with depression a common genetic vulnerability, and the comorbid condition creates an additional disability burden. Langer and Rodebaugh suggest that, unlike some of the other anxiety disorders, SAD would seem to more commonly predate depression than the other way around, pointing to the possibility that SAD may be an important causal factor in some instances of major depression. They suggest that the common vulnerability may be the presence of an excessive belief that one is *not good enough*. This belief is very common among depressed persons and certainly is common among individuals with SAD in the context of social situations. It remains to be seen whether, in dealing with adolescents, interventions that mitigate the likelihood of developing these dysfunctional beliefs could be preventative for social anxiety and major depression. Research evaluating such programs among youngsters of high school age should be pursued.

As in the case of the other anxiety disorders, comorbidity with major depression is found in the majority of individuals with panic disorder (Chapter 6). This comorbidity results in greater social disability, greater persistence of the disorder, more severe occupational impacts, and higher suicide rates, much as with other anxiety disorders comorbid with depression. Castriotta and Craske (Chapter 6) note that risk factors for depression and panic disorder are similar (e.g., personality trait of neuroticism and vulnerability to experiencing negative affect that have been identified in genetic and phenotypic research). The epidemiological literature indicates that panic attacks are often evident before the first episode of major depression. However, panic disorder more often develops after the first episode of major depression, suggesting that depression may play a crucial role in the evolution of occasional panic attacks to full syndromal panic disorder. Again, interventions may be deployed to individuals who have recently experienced panic attacks as a way of intervening early and preventing first episodes of depression and panic disorder.

In sum, the anxiety disorders share a great deal in common with depression with respect to their etiology, symptom presentation, treatment, and long-term consequences. Moreover, their comorbid presentation usually suggests that each disorder will have a more severe presentation and poorer prognosis than the either one of the two disorders presenting separately. All of these features suggest that early and sustained interventions at the first sign of either depression or an anxiety disorder might head off the development of a comorbid condition and break what appears to be a reciprocal cycle of depression and anxiety comorbidity.

Disease Burden

Depression is associated with increases in disease-related morbidity and mortality. For example, chronic health conditions often require patients to undertake treatment regimes that are difficult, unpleasant, and unremitting. There is evidence across many chronic health conditions that depressed patients are less adherent to their treatments than nondepressed patients. In disorders such as HIV/AIDS, MS, CHD, and kidney disease, nonadherence can lead to disease complications and early death. When depression is present in the context of other psychiatric disorders (including the personality disorders), it is often the case that both disorders (or more) show more severe symptoms and are more difficult to treat. Although transdiagnostic treatments (Moses & Barlow, 2006) are being developed and deployed, more research that addresses effective treatments for comorbid depression is clearly needed.

Assessment Issues

All of this volume's contributors address assessment issues with respect to their focus on other psychiatric disorders, chronic health conditions, disturbed personal relationships, and treatment. For example, what is the role of internalizing liability in assessment? This question is posed by Eaton and Krueger (Chapter 5) and bears heavily in the assessment of the comorbidity of depression and anxiety

disorders. But it also extends to personality disorders, for example, and it may have implications for identifying potentially effective treatments that address core internalizing in depression and other disorders. Another issue raised by Eaton and Krueger is that of differential item functioning (DIF). This issue comes to the fore most prominently in the diagnosis of depression in chronic health conditions. As noted earlier, there are many depression symptoms that are common manifestations of chronic health conditions such as coronary heart disease, cancer, AIDS, and kidney disease. The DSM assumes that all symptoms are weighted the same in making a diagnosis of depression. DIF allows for the possibility that some symptoms might be weighted more or less in making a diagnosis of depression in a particular population, such as patients with heart disease or cancer or even schizophrenia or a personality disorder. As an example, a patient with cancer undergoing chemotherapy might have enough symptoms to merit a diagnosis of depression, but a careful assessment might reveal that many of the "depression" symptoms present are not strongly related to a diagnosis of depression. So, for example, the clinician might weigh depressed mood, guilt or worthlessness, and suicidal ideation more heavily than symptoms like fatigue and appetite disturbance. In sum, there are opportunities for improving the identification of depression in individuals suffering from other psychiatric and chronic health conditions and using that information to guide effective treatments.

A related but separate issue is that of screening for depression in the context of chronic medical conditions. Despite the high prevalence of depression in many chronic health conditions, screening for depression in the context of routine care of CHD, AIDS, MS, or kidney disease, for example, remains controversial. The U.S. Preventive Services Task Force (2009) recommends only screening for depression when there are adequate supports that allow for effective referral, adequate treatment, and follow-up. While these requirements are perhaps more likely to be met in the context of specialized care for serious chronic health conditions, there is no guarantee that patients will follow through and access evidence-based treatments because of stigma, cost, and practical access barriers. Further research is needed to determine the most effective methods to bridge the gaps between screening, assessment, and treatment.

Treatment Issues

Treatment of depression comorbid with other psychiatric disorders, chronic health conditions, or disturbed relationships is usually more complex than the treatment of depression alone. Chapters 35, 32, and 31, on cognitive therapy, community based interventions, and multidisciplinary treatment respectively, address these issues from very different perspectives. For example, Whisman and BE (Chapter 35) suggest that cognitive therapy for depression may be differently implemented depending upon whether the comorbid condition is believed to be an independent disorder, one with a common etiology, or one that causes or is caused by the depressive disorder. Alterations in treatment include changing treatment parameters (longer sessions, more frequent sessions, or more sessions). Another alteration would entail modifying the style of presentation of cognitive therapy, recognizing that patients with differing personality pathology may prefer a supportive versus goal-directed emphasis (or vice-versa) in cognitive therapy. A third alteration would entail augmenting standard cognitive therapy with other interventions targeted to the comorbid condition (e.g., introducing emotion regulation and distress tolerance skills from dialectical behavior therapy) for a patient with comorbid depression and borderline personality disorder. Other intervention modalities can be introduced in parallel or sequentially. While these sorts of adaptations seem useful and intuitive, Whisman and BE point to research suggesting that adding additional elements to cognitive therapy for depression may dilute its potency. Finally Whisman and BE provide guidance on adapting to cognitive therapy to several comorbidities including anxiety disorder, substance abuse disorders, and personality disorders. These recommendations reflect the expert opinions of investigators who work with these disorders, but very few of them are based on evidence from randomized controlled trials. Such trials are clearly needed.

Gitlin highlights the importance of community- and home-based interventions (Chapter 32) in the context of late-life depression. This approach emphasizes the importance of embedding interventions in an environment that is familiar and acceptable to an older adult, particularly one who might be cognitively compromised. In many ways, this approach is bringing mental health care full circle, particularly in cases where individuals are not so impaired as to require inpatient care. These interventions are often delivered by nurses or social workers who are accustomed to delivering care in community settings and homes. Moreover, they have also been used successfully with populations extending beyond the

aged. For example, home- and community-based interventions are increasingly being delivered to high-risk pregnant and postpartum women as a way of increasing the likelihood of positive outcomes for both mothers and babies (see Chapters 30 and 33) (Ammerman et al., 2013; Segre, Stasik, O'Hara & Arndt, 2010). In some cases the comorbid condition is a chronic health condition such as dementia or some other disabling condition associated with aging; in other cases it may be a nonchronic health condition such as pregnancy. In all of these cases, comorbid depression complicates adjustment efforts and leads to significant disability. Gitlin offers several recommendations including research on the refinement of depression interventions, on the adequacy of depression screening, and on how to successfully implement these programs in the community. Added to this research agenda is the need for cost analyses of community- versus clinic-based care, particularly in light of the mandates of the Affordable Care Act (i.e., "Obama Care") in the United States.

Of course, psychological interventions are not always sufficient or desired in cases of depression comorbidity. Howland (Chapter 31) provides a comprehensive review of medical approaches to the management of treatment resistant and comorbid depression. Howland makes several important observations. First, many of the medications that have been approved for the treatment of depression also are approved for the treatment of frequent comorbid conditions, particularly the anxiety disorders. The implication is that medication monotherapy may be appropriate for some comorbid depression conditions. Second, other medications may be used to augment antidepressant medications. Howland argues that thyroid hormone, lithium, and second-generation antipsychotics are the best studied and validated in placebo-controlled trials. Finally, combination psychotherapy and pharmacotherapy is often recommended for more serious and comorbid depressions despite the rather limited evidence for its effectiveness relative to one treatment or the other. Howland argues for comparative effectiveness studies that include assessments of efficacy, tolerability, safety, acceptability, and cost across interventions that target comorbid depression.

The chapters on chronic health conditions document hundreds of clinical trials addressing depression as a comorbid condition. On balance, these trials document the relative effectiveness of evidence-based treatments for depression in the context of the various chronic health conditions. Nevertheless, critics have frequently pointed to the poor methodological quality of many of these trials and to the fact that a depression diagnosis is often not necessary for a patient's inclusion in a trial. Despite the evidence that depression is associated with increased morbidity and mortality in chronic health conditions, there is little evidence that evidence-based depression treatments significantly impact these two important health indicators.

Conclusion

The inescapable conclusion in reading the chapters in this volume is that depression is a very common complication of myriad other conditions that afflict men, women, and children. Depression usually makes other disorders more difficult to treat, often because depressed patients are poor in their adherence to treatment. Depression creates a greater disease burden. And finally, depression usually signals a poorer prognosis for patients with other disorders and relationship conflict. For all of these reasons, the research agenda bearing on depression comorbidity with respect to etiology and treatment is a large one, one that is well articulated by the contributors to this volume.

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