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# A Neglected Condition

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Despite being common and impairing, bipolar II disorder (BD II) is a neglected condition. Using conservative estimates, studies show that BD II affects approximately 0.4% of the population (Merikangas et al. 2011) and causes significant suffering and functional difficulties (Rosa et al. 2010; Ruggero et al. 2007). Evidence supports that BD II exists as a phenotype, distinct from bipolar I disorder (BD I) and other spectrum bipolar conditions (American Psychiatric Association 1994). But compared with BD I, we know far less about BD II and how to treat it. Clinicians may not recognize the illness, and many do not know how to manage it. Consequently, thousands are unaware they have BD II and receive no treatment or inappropriate treatment.

This book provides a comprehensive overview of our current understanding of BD II. We review phenomenology, discuss biologic underpinnings, and summarize management strategies to provide readers with state-of-the-art knowledge about BD II. By increasing awareness of BD II and disseminating information about it, we hope that more people will get the right diagnosis and receive appropriate treatments sooner. Because BD II is a neglected condition, however, there are many gaps in our knowledge. We hope, therefore, that this book will also encourage research that may ultimately lead to better recognition, understanding, and treatment of BD II.

In this chapter we introduce BD II, including its clinical importance and historical origins. We then describe the four main topic areas of the book: recognition, understanding, treatment, and special populations. A case vignette at the end of this chapter illustrates the main themes explored in this book through the lived experiences of someone with BD II. Throughout this book, all names, details, and identifying information have been changed to ensure patient privacy.

## Why Is the Bipolar II Subtype Important?

Despite its relatively late arrival on the diagnostic scene, BD II has public health significance. Associated with morbidity comparable to that of BD I (Forte et al. 2015), BD II is characterized by marked impairment in psychosocial functioning (Rosa et al. 2010), a chronic course of illness (MacQueen and Young 2001), and high rates of suicide (Novick et al. 2010). Cognitive impairment is common (Torrent et al. 2006), and multiple comorbidities are the rule rather than the exception (Merikangas et al. 2011). Economic burden associated with BD II is four times higher than that associated with BD I (Dilsaver et al. 2011).

Absent the pathognomonic feature of mania that makes BD I among the most easily identified psychiatric disorders (Regier et al. 2013), BD II is admittedly less dramatic than BD I but no less impairing. Some erroneously refer to it as a "less severe" form of bipolar disorder, but that is a misnomer. BD II is characterized by multiple recurrent depressive episodes punctuated by infrequent hypomanic episodes. In one longitudinal study, the ratio of depressive to hypomanic episodes over time was 3:1 (Kupka et al. 2007). Thus, the BD II phenotype is dominated by depression, which, although less striking than mania, can be the more problematic pole of the disorder (Drancourt et al. 2013; Hlastala et al. 1997). Bipolar depression is notoriously difficult to treat and drives much of the morbidity and mortality associated with bipolar disorder (Kessler et al. 2006).

BD II is also important because it is overlooked. Hypomania, the sine qua non of BD II, may be difficult to elicit from those who perceive these episodes as "positive," leading to an overdiagnosis of major depressive disorder (MDD). Many clinicians also do not recognize the energized depressions that occur in the context of depression with mixed symptoms. It takes, on average, 5 years for individuals to receive an accurate diagnosis of BD I, but over 10 years for those with BD II to receive an

accurate diagnosis (Drancourt et al. 2013; Ghaemi et al. 2000). Thus, individuals with BD II often suffer for more than a decade with an inaccurate diagnosis and inappropriate care.

## Why Is Bipolar II Disorder Misunderstood and Overlooked?

Bipolar disorders, including BD II, are characterized by fluctuating mood states. Descriptions of individuals who experience alternating periods of elevated and low moods have been documented since the Greco-Roman period (Jackson 1986). Modern conceptualizations of bipolar disorder, however, began in part with the German psychiatrist Emil Kraepelin in the early twentieth century (Goodwin and Jamison 2007). Kraepelin, working with European colleagues to catalog and classify abnormal human behavior, developed two categories to describe chronic psychotic disorders based on episodicity and course. *Dementia praecox* (later renamed *schizophrenia*) was used to characterize nonepisodic psychotic disorders with a poor prognosis. *Manic-depressive illness* was defined as an episodic condition (i.e., characterized by discrete mood episodes followed by symptom-free intervals) with a comparatively benign prognosis (relative to dementia praecox). The manic-depressive illness category included those with recurrent mood episodes, be they manias or depressions.

By the middle of the twentieth century, phenomenologists advanced the concept of a bipolar-unipolar dichotomy based on the presence or absence of a prior history of mania. Thus, individuals with recurrent depressive episodes and at least one episode of mania were placed in the bipolar category; those with depression only (recurrent or not) were placed in the unipolar category (Leonhard 1979). In the United States, these concepts were reified in the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III; American Psychiatric Association 1980). Thus, individuals with depression were diagnosed with either unipolar disorder or bipolar affective disorder, depending on whether or not they had a prior episode of mania.

In the 1960s, David Dunner became interested in patients who did not belong in either the unipolar or bipolar affective disorders category. Examining data from depressed patients who had been hospitalized at the National Institute of Mental Health, Dunner and colleagues identified

"an interesting group of subjects who had been hospitalized for depression and who clearly had hypomanic but not manic episodes" (Dunner 2017, p. 520). He coined the term *bipolar II disorder* to describe these individuals' illness. These individuals were distinct from those with BD I by virtue of never having had a manic episode, and distinct from those with unipolar disorder by virtue of having had at least one hypomanic episode. Patients with BD II were as likely as those with BD I and more likely than those with unipolar disorder to have relatives with histories of mania. These patients also had higher rates of suicide compared with the other groups (Dunner et al. 1976). Because of data showing differences from BD I in clinical features, family history, longitudinal illness course, and outcomes with pharmacology, BD II was officially recognized in 1994 as a distinct disorder in DSM-IV (American Psychiatric Association 1994). The World Health Organization's International Classification of Disorders recognized BD II in its 10th and most recent revision (ICD-10), which was gradually released globally during the first decade of the twenty-first century.

The phenomenology of bipolar disorder was first described in the fifth century B.C.E., but BD II was not formally recognized until 1994. Thus, for almost 2,500 years, BD II was subsumed under nonspecific categories such as manic-depressive illness, unipolar disorder, and bipolar affective disorder. Until Dunner and colleagues described evidence of biologic, genetic, and clinical differences between BD I and II, little information was available about those with alternating depression and hypomania only. Without an operationalized diagnosis, research was not conducted on BD II treatments. Thus, it is not surprising that little was known about this population before 1994. But even once the diagnosis was formalized, the field of psychiatry has been slow to catch up. The admittedly subtle distinctions between mania and hypomania are confusing for clinicians and patients alike. Clinicians used to the framework of unipolar depression versus bipolar affective disorder are slow to adopt new concepts, such as an intermediary BD phenotype. Nuanced understanding of psychopathology is needed to make a correct diagnosis of BD II. Researchers and pharmaceutical companies have been reluctant to wade into this "messy" disorder, limiting accumulation of new evidence about BD II. Thus, the halo of misunderstanding and misinformation about BD II persists, even though BD II has been recognized as a distinct phenotypic entity for a quarter century.

## How Is This Book Organized?

This book is divided into four parts: recognition, understanding, treatment, and special populations. Below we describe each of the four book parts, summarizing themes covered and pointing the reader to individual chapters on specific topics.

### Part I: Recognition

Part I grapples with the thorny issues of BD II diagnosis and comorbidities. Diagnosis of BD II can be difficult and can be made even more complicated by the fact that psychiatric comorbidity is the rule rather than the exception. These factors have important implications for course and outcome. Part I focuses on differential diagnosis, medical and psychiatric comorbidities, and risk for suicide.

Diagnosis of BD II is somewhat controversial. Conceptually, some authors favor a *spectrum* view of mood disorders, positioning BD I at one end of the continuum and MDD at the other end, with recurrent depression plus any other feature of bipolarity (i.e., hypomania, family history of mania, antidepressant-induced mania, poor antidepressant response) in the middle (Ghaemi et al. 2002). This model invokes the conceptualization of Kraepelin, who identified mood episode *recurrence* (rather than mood episode *type*) as the most salient feature of these illnesses. Others favor a categorical approach to diagnosis, identifying BD I, BD II, and MDD as distinct entities that are distinguished by presence or absence of mood episode *types* (mania, hypomania). This latter approach is used in clinical practice and is codified currently in DSM-5 (American Psychiatric Association 2013). Because DSM-5 provides a common language for identifying patients and, more importantly, identifies groups that have well-characterized epidemiology, outcomes, and treatment response, we use DSM-5 criteria in this book. We anticipate that with further advances in understanding the biology of bipolar disorder, DSM will continue to evolve. Although the future is hard to predict, it seems unlikely that the categories of BD I, BD II, and so forth will ever fully lose their utility.

Differential diagnosis of BD II using DSM-5 criteria is a nontrivial matter. As previously discussed, hypomania may be underreported by patients, who do not perceive it to be a problem or simply do not recognize it as a distinct mood state, leading to an overdiagnosis of MDD. Hypomania can also be difficult to distinguish from mania, leading to

potential misdiagnosis of BD II as BD I. Careful review of symptomatology, illness course, family history, and treatment response is an important part of the BD II diagnostic assessment. These issues are discussed in depth in Chapter 2, "Diagnosing Bipolar II Disorder."

Distinguishing BD II from borderline personality disorder (BPD) represents a different type of challenge (Zimmerman et al. 2013). As discussed in Chapter 3 ("Interface Between Borderline Personality Disorder and Bipolar II Disorder"), both disorders are characterized by mood instability, chronic illness course, suicide risk, irritability, lability, and interpersonal difficulties. Transient episodes of affective instability and emotional lability associated with BPD may be mistaken for hypomanic episodes. To make matters more complicated, these conditions often co-occur; about 20% of individuals with BD II also have BPD (Zimmerman and Morgan 2013). Improved familiarity with diagnostic criteria and increased understanding of the sources of diagnostic error can help improve diagnostic accuracy, ultimately leading to better ability to distinguish BPD from BD II.

In addition to risk for BPD, individuals with BD II are at increased risk for multiple psychiatric comorbidities. Indeed, comorbidity is the rule rather than the exception in BD II. Almost all individuals with BD II have at least one psychiatric comorbidity, and over half have at least three (Merikangas et al. 2011). Anxiety disorders co-occur most commonly with BD II, followed by impulse-control disorders and substance use. Similarly, almost all individuals with BD II have at least one medical comorbidity, and about 40% have at least three (Sylvia et al. 2015).

Both BD I and II are associated with elevated risk for cardiovascular disease and metabolic/endocrine disorders, with these comorbid conditions occurring more frequently than in the general population. Although rates of cardiometabolic disorders are similar in BD I and BD II (Amann et al. 2017), individuals with BD II appear to be at greater risk for gastrointestinal disorders (Forty et al. 2014), perhaps related to dysfunction of the gut microbiota.

Because most individuals with BD II experience many other illnesses in addition to their mood disorder, developing strategies to identify and address comorbidities is essential to the clinical management of BD II. Chapter 4 ("Psychiatric and Medical Comorbidities With Bipolar II Disorder") describes psychiatric and medical comorbidities associated with BD II and proposes strategies to address them.

Patients with BD II are also at increased risk for suicide attempts and completion. Risks for suicide attempts and completed suicide in BD II are at least comparable to those in BD I and are much higher than those in the general population (Novick et al. 2010). Chapter 5 ("Suicide and Bipolar II Disorder") describes a framework for understanding risk and a clinical model for conducting a BD II–specific suicide risk assessment. The authors of this chapter underscore factors associated with increased risk in BD II and identify strategies to mitigate risk.

## Part II: Understanding

Part II focuses on the biologic determinants of BD II. A growing body of evidence suggests that the underlying biology of BD II is distinct from that of other mood disorders (BD I, MDD). The genetics of psychiatric disorders are complex and multifactorial, and BD II is no exception. Risk for psychiatric diseases, including BD II, appears to represent a manifestation of broad-based susceptibility coupled with environmental risk factors (Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium 2018). As reviewed in Chapter 6 ("Genetics of Bipolar II Disorder"), increased understanding of polygenic risk coupled with improved recognition of other determinants of disease will, it is hoped, improve specificity in disease prediction models in the future (Brainstorm Consortium et al. 2018).

BD II is characterized by abnormalities in the neural systems that subsume reward and cognitive control of emotion regulation. Neuroimaging studies show similar alterations in brain regions responsible for reward anticipation, reward processing, and executive function in individuals with BD I and II in comparison to healthy control subjects (Phillips and Swartz 2014). Some differences are noted between BD I and II, however. For instance, differences were found between BD I and II in the ventral striatum in response to reward anticipation, with BD II patients having significantly greater left putamen volume, which in turn correlated positively with left ventral striatal activity to reward (Caseras et al. 2013). As discussed in Chapter 7 ("Functional Brain Imaging and Neural Determinants in Bipolar II Disorder"), neuroimaging may play an increasingly important role in the diagnosis and understanding of BD II as this research progresses.

## Part III: Treatment

Part III focuses on how to better manage BD II. It provides an up-to-date review of medication options and psychosocial treatments for patients with BD II. Chapters 8, 9, and 10 summarize both what is known and what is not known about current treatments for BD II and point toward next steps needed to develop even better management strategies for BD II.

For many years, individuals with BD II have been treated as if they have BD I, that is, with mood-stabilizing medications, including antipsychotic medications, as the mainstay of treatment. What is the evidence supporting this approach? What is the role of medications such as lithium, divalproex, lamotrigine, and carbamazepine in the management of BD II? What about the atypical antipsychotic medications? Chapter 8 ("Mood Stabilizers and Antipsychotic Medications in Bipolar II Disorder") reviews evidence needed to answer these questions and provides clinical examples of how to use these medications for patients with BD II.

Historically, antidepressant medication has been viewed with suspicion as a treatment for BD, including BD II. Recent data, however, show that antidepressant monotherapy may be superior to lithium as a treatment for BD II depression (Amsterdam et al. 2016). Chapter 9 ("Antidepressant Medications in Bipolar II Disorder") reviews controversial evidence about antidepressant use (including as monotherapy) for BD II, weaving in clinical examples.

Psychosocial interventions play an important role in the management of BD II, both as medication augmentation strategies and, as supported by recent studies, as an alternative to medication (Swartz et al. 2018). Chapter 10 ("Psychosocial Interventions in Bipolar II Disorder") reviews evidence-based psychosocial interventions for BD II, focusing on novel recent information showing that for some individuals with BD II, psychotherapy alone may suffice. A case vignette describing treatment of BD II with interpersonal and social rhythm therapy (IPSRT; Swartz et al. 2012) is presented.

## Part IV: Special Populations

We recognize the irony in identifying women (who make up 50% of the population) and children and adolescents (who at one point in time are appropriate classifiers for 100% of the population) as "special" populations. We do not wish to imply that the material in Parts I through III does not apply to these large groups; rather, the intent of Part IV is to cover issues specific to these populations that were not discussed in earlier parts.

Chapter 11 ("Bipolar II Disorder in Childhood and Adolescence") brings us up to date on current thinking around the evolution of BD II from childhood through early adulthood. This chapter grapples with the challenges of diagnosing and managing BD II in youth. Mood instability, a defining feature of BD II, often begins in childhood. For some, the mood instability in childhood does not progress and thus perhaps represents a distinct phenotype from that seen in individuals at risk for BD II in adulthood. Because early presentations may not be the final state of illness, there may be discontinuities in diagnosis between childhood and adulthood. For instance, one longitudinal study of at-risk youth found that in approximately 25% of those with BD II, the disorder had converted to BD I by 4-year follow-up, and in 35% of youth with BD not otherwise specified (NOS), the illness had converted to BD II (Axelson et al. 2011). There are no randomized controlled trials of treatments for youth with BD II, but potential strategies for managing these children and adolescents are discussed.

Management of BD II in women during reproduction transitions poses special challenges. Women with BD II are more likely to experience menstrual cycle–related mood worsening relative to those with BD I and MDD (Joffe et al. 2006) and, in pregnancy, are more likely than women with BD I to stop medication, experience episode recurrence, and have a depressive or mixed episode (versus a euphoric hypomanic episode) (Driscoll et al. 2017). Chapter 12 ("Reproductive-Age Women With Bipolar II Disorder") discusses the challenges women with BD II face in the context of reproductive transitions such as pregnancy, childbirth, lactation, and the menstrual cycle. Chapter 12 proposes a personalized decision-making framework to address the complexity of managing BD II during these epochs. Hormonal contraception is explored for stabilization of mood symptoms across the menstrual cycle and in the context of potential drug-drug interactions when coadministered with mood-stabilizing medication. Case material illustrates clinical decision-making and management strategies.

## Case Vignette

Tina is a 30-year-old web designer. She supports herself performing odd web design jobs for small companies. She was admitted to inpatient psychiatric services following an ingestion of old prescription medications, deemed a suicide attempt by self-poisoning. She stated that the self-