Lois W. Choi-Kain
John G. Gunderson *Editors*

Borderline Personality and Mood Disorders

Comorbidity and Controversy

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Preface

In the roughly 40 years during which the relationship of borderline personality disorder (BPD) to mood disorders has been the topic of research and debate, there has been significant progress. Still, questions persist. This book will review that progress and will identify those questions. These comments provide an introduction.

In the late 1960s, BPD was introduced primarily as a psychoanalytic construct, which was enthusiastically adopted by the burgeoning psychotherapeutic community. This birthing coincided with the emergence of psychopharmacological treatments for depression, bipolar disorder, and schizophrenia. After becoming official in the DSM-III, BPD was considered a variant of all three. Research easily identified significant descriptive, genetic, and prognostic distinctions of BPD from schizophrenia. The identification of schizotypal personality disorder was a byproduct. No such closure was forthcoming with respect to mood disorders. Based on the results of his research [1, 2], Akiskal portentously announced that "borderline personality disorder was an adjective in search of a noun" [3].

In the 1980s, research about this issue mushroomed. In 1985, a review of the emerging evidence based on the Robbins & Guze criteria for diagnostic validity concluded that this evidence did not confirm either that BPD caused mood disorders or vice versa [4, 5]. Nor did it confirm their independence. The disappointingly complicated conclusion was that neither the mood disorder criteria—both major depressive disorder (MDD) and bipolar disorder—nor the BPD diagnostic criteria were adequately specific and the resulting co-occurrence was due to the heterogeneity within these diagnoses. Thus, more research was needed.

In 1991, 6 years after that initial review, conclusions about this interface were revised [6]. By 1991, bipolar disorder and MDD had established such phenomenological and therapeutic distinctions that research focused on the relationship of BPD to each as separate entities. Particular attention was now being paid to BPD's interface with MDD due to the high prevalence of both disorders in clinical settings and to the remarkably high rates of their co-occurrence (generally 50 % cross successfully and 75 % lifetime). New data showed that the high rates of co-occurring MDD in BPD patients and in their relatives was nonspecific, i.e., rates of MDD were just

as high in patients and relatives with other personality disorders [7–9]. New evidence also identified more family dysfunction, conflict, and childhood abuse in the development of BPD than of MDD. Finally, it was now clear that BPD patients were far less responsive to antidepressants (or mood stabilizers) than were mood disorder patients. Thus, the growing evidence showed a weak and nonspecific relationship between these disorders. Though, in retrospect, the quality of the available research in 1991 could be faulted, this conclusion about BPD's independence from MDD received no serious challenges for the next 20 years. During those 20 years (1990–2010), many hundreds of NIMH- and PHARMA-funded trials were conducted about the efficacy of various antidepressants for MDD. However, these trials rarely examined the effects of co-occurring BPD, and pharmacological research was comparatively absent for BPD. Psychiatry had split the disorders with BPD in the province of psychology and MDD in the province of psychopharmacology.

Those 20 years saw dramatic shifts in psychiatric practices. The generation of psychiatrists trained after 1980 were now oriented toward a biological understanding for psychiatric disorders and had increasingly begun to see their primary clinical role as providers of medications. In this context, the idea of a broad spectrum of bipolar disorder, notably still championed by Akiskal [10–12], that were potentially treatable with mood stabilizers was widely adopted. The empirical support for this expansive claim was modest to say the least [13, 14], but the idea's appealing conceptual base and clinical implications dramatically increased bipolar diagnoses and mood stabilizer prescriptions [15].

Ironically, even as the bipolar diagnoses and psychopharmacological therapies were both expanding, empirically based psychosocial treatments were showing dramatic success in treating borderline patients. Psychiatrists, however, were no longer being trained to provide such treatments.

This is the background against which this book revisits the question of how BPD relates to MDD and to bipolar disorders. Readers will be surprised, as we have been, by the range and quality of research that newly informs this issue. It will certainly be confirmed that BPD's relationship to MDD is quite distinct from its relationship to bipolar disorders. While BPD's independence from bipolar disorders seems surprisingly clear on the basis of family studies and their relatively modest effect on each other's course, bipolar II might seem to share much with BPD in terms of course, drug response, and developmental adversities. The relationship of BPD to MDD emerges with renewed complexity. There is now much evidence of shared neurobiology, and the negative effects on each other's course also suggest overlapping psychopathology. And even though BPD's depression has still not shown much responsiveness to antidepressants, the results from STAR*D show that even most patients with MDD do not benefit from them [16]. This complexity is closer to what was first suggested in the 1985 review than it is to the independence that seemed evident in 1991.

The authors of this book will review the last two decades of progress in scientific inquiry about the relationship between mood and personality disorders and the influence of this empirical data on our ways of conceptualizing and treating them. Paris opens the book with an introduction defining general trends both influencing the expansion of the mood disorder spectrum and undermining clinical recognition and

focus on personality disorders. Goodman and collaborators then review the overlaps and differences between MDD and BPD in phenomenology and biological markers, followed by a review by Choi-Kain and Rodriguez-Villa of the overlaps and distinctions between more atypical mood disorder variants (e.g., atypical depression and cyclothymia) and BPD. Chapters by Zimmerman and Morgan, Ghaemi and Barroilhet, and Reich review the current state of thinking on the distinctions between bipolar disorder and BPD, with attention to problems of misdiagnosis and use of clinical vignettes to illustrate important distinguishing features. Chapters by Lara and collaborators and Yalch, Hopwood, and Zanarini review two models explaining the relationship between mood, temperament, and personality. This is followed by Chanen and Thompson's review of the literature on risk factors and early signs of BPD and mood disorders in childhood through young adulthood and a review of the longitudinal studies on BPD and mood disorders by Andrew Skodol. The last segment of the book includes three chapters on treatment. Silk summarizes the literature on the psychopharmacological management of depression in BPD. The chapters by Jacob and Rodriguez-Villa as well as Luyten and Fonagy present flexible cognitive behavioral and mentalizing approaches to mood disorders and BPD that might be more well suited to the general mental health practitioner than the highly intensive specialized approaches that are empirically validated for BPD. The book closes with a conclusion with a synthesis of the current status of thinking on the relationship between mood and borderline personality disorder. In summary, all the authors contribute to a sense that the evolving dialogue between the mood and personality disorder realms of psychiatry has moved away from contentious debate and toward the possibility of synthesis, providing increasing clarity on the relationship between mood and personality to inform improvements in the clinical management of the convergence of these psychiatric domains in common practice.

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References

1. Akiskal HS. The nosologic status of borderline personality: clinical and polysomnographic study. Am J Psychiatry. 1985;142(2):192–8.
2. Akiskal HS, Chen SE, Davis GC, Puzantian VR, Kashgarian M, Bolinger JM. Borderline: an adjective in search of a noun. J Clin Psychiatry. 1985;46(2):41–8.
3. Akiskal HS. Borderline: an adjective in search of a noun. In: Silver D, Rosenbluth M, et al, editors. Handbook of borderline disorders. Madison: International Universities Press, Inc; 1992.
4. Robbins E, Guze SB. Establishment of diagnostic validity in psychiatric illness: its application to schizophrenia. Am J Psychiatry. 1970;126:983–7.
5. Gunderson JG, Elliott G. The interface between borderline and affective disorders. Am J Psychiatry. 1985;142:277–88.
6. Gunderson JG, Phillips KA. A current view of the interface between borderline personality disorder and depression. Am J Psychiatry. 1991;148(8):967–75.

7. Zanarini MC, Gunderson JG, Marino MF, Schwartz EO, Frankenburg FR. DSM-III disorders in the families of borderline outpatients. J Personal Disord. 1988;2.
8. Zanarini MC, Gunderson JG, Frankenburg FR. Axis I phenomenology of borderline personality disorder. Compr Psychiatry. 1989; 30(2):149–56.
9. Zanarini MC, Gunderson JG, Frankenburg FR, Chauncey DL. The revised diagnostic interview for borderlines: discriminating BPD from other Axis II disorders. J Personal Disord. 1989;3.
10. Akiskal HS. The prevalent clinical spectrum of bipolar disorders: beyond DSM-IV. J Clin Psychopharmacol. 1996; 6:4S–14S.
11. Akiskal HS. The bipolar spectrum: the shaping of a new paradigm in psychiatry. Curr Psychiatry Rep. 2002;4:1–3.
12. Akiskal HS, Hantouche EG, Allilaire JF. Bipolar II with and without cyclothymic temperament: "dark" and "sunny" expressions of soft bipolarity. J Affect Disord. 2003;73:49–57.
13. Paris J, Gunderson JG, Weinberg I. The interface between borderline personality disorder and bipolar spectrum disorders. Compr Psychiatry. 2007;48:145–54.
14. Zimmerman M, Ruggero CJ, Chelminski I, Young D. Is bipolar disorder overdiagnosed? J Clin Psychiatry. 2008;69(6):935–40.
15. Day M. Drug industry is partly to blame for overdiagnosis of bipolar disorder, researchers claim. BMJ. 2008;336(7653).
16. Warden D, Rush AJ, Trivedi MH, et al. The STAR*D Project results: a comprehensive review of findings. Curr Psychiatry Rep. 2007;9:449–59.

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Part I
Introduction

Chapter 1
Mood Disorders and Personality Disorders: Simplicity and Complexity

Joel Paris

Mood and Personality

Mood is a relatively straightforward concept. For the most part, mood varies as to whether it is high, low, or unstable. In contrast, personality is a very complex construct. It describes traits that affect behavior, thought, and emotion. Since personality describes normal variations, as opposed to abnormal states of mind, it is difficult to separate personality disorder (PD), which only some people have, from personality, which everyone has. Another difference is that while depressed or manic mood states can be scaled by clinicians, personality is often measured by self-report systems derived from factor analysis, such as the five-factor model [1], or by an extensive list of traits that can be clinically rated, as in DSM-5 [2]. Finally, mood disorders are often treated with drugs, while personality disorders usually require psychotherapy. For all these reasons, the construct of a mood disorder more readily appeals to clinicians who are looking for targets for treatment, while a personality disorder is seen as a murky and problematic idea.

Why the Mood Disorder Spectrum Has Expanded

Diagnostic constructs in psychiatry often reflect currently popular treatment options. Fifty years ago, a wide variety of clinical syndromes, most particularly somatic symptoms, were seen as reflections of abnormal mood or "masked depression" [3]. That diagnosis emerged at the same time as the wide use of tricyclic antidepressants

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and supported more frequent diagnoses of mood disorder [4]. Physicians naturally favor making diagnoses that lead to a prescription. Even then diagnoses that were indications for psychotherapy, an option that has always been expensive and not readily available, were less popular.

Theoretical ideas about mood disorders have also supported expansion of their scope. Forty years ago, Akiskal and McKinney [5] published a widely cited paper in *Science* arguing that depression was a single entity that only varies in severity. This construct was influential in the shaping of diagnostic manuals and supported the practice of treating a wider range of patients with antidepressants, a trend further strengthened by the development of selective serotonin reuptake inhibitors. At the same time, psychopathology of all kinds has been seen in the light of variations in mood [6].

Depression and Personality Disorder

While research on depression has been active from the 1950s, systematic empirical studies of personality disorders began to appear only in the 1980s [7]. At the time, mood disorder specialists challenged this research on the grounds that PDs could be better understood as depressive variants. Akiskal et al. [8] dismissed the diagnosis of borderline personality disorder (BPD), suggesting archly that since there was no border on which one could be "borderline," this term was "an adjective in search of a noun." Instead, Akiskal recommended that it be treated in much the same way as depression, i.e., with drugs. A counterattack from BPD specialists [9] argued that mood instability is a different phenomenon from sustained low mood. Moreover, evidence failed to show that antidepressants are particularly helpful in BPD [10]. Yet pharmacological treatment for these patients, not to speak of all psychiatric patients, became ubiquitous. To understand this shift in practice, we need to examine changes in the ideology of psychiatry as a medical specialty.

Psychotherapy and Psychopharmacology

Psychiatry used to be closely identified with psychotherapy. (Even today, the image of a bearded analyst behind a couch continues in New Yorker cartoons.) But beginning in the 1970s, the specialty underwent a paradigm shift [11]. Psychotherapy, in particular psychoanalysis, was seen as unscientific and retrograde. Since then, psychotherapy has been driven to the periphery of the profession. The new paradigm for psychiatry has been based on neuroscience, with treatment redefined as the clinical application of these principles [12]. Psychopathology would now be understood as a problem in neurochemistry or neurocircuitry and treated accordingly, largely with pharmacological interventions.

These conclusions were strongly supported by the pharmaceutical industry and by key opinion leaders drawn from academic psychiatry, who are often supported

by the industry [11]. One cannot deny that in choosing interventions for psychiatric patients, money talks. One never sees advertisements in journals supporting psychotherapy. In contrast, each of the latest antidepressants is heavily marketed, even if they differ by only a few atoms from those that have been used for years.

This trend led to the theoretical dominance of neurobiology and a decline in the provision of psychotherapy in psychiatry [13]. It supported diagnoses of mood disorders, which are widely understood to derive from abnormalities of neurotransmission that can be corrected by pharmacotherapy. It undermined interest in personality disorders, seen as poorly defined concepts treated with psychotherapies of doubtful value.

Moreover, patients themselves often prefer to be diagnosed with mood disorders. They may see depression (or bipolarity) as validating—a "chemical imbalance" for which they are not responsible. For some, personality disorder is seen as stigmatizing, implying they have a "bad personality." It is possible to explain to patients what a personality disorder is and to reassure them that their condition is *less* chronic than many mood disorders, since research shows that most patients can be expected to get better with time [14]. But while some appreciate this feedback, particularly when antidepressants have not helped, others prefer a diagnosis of mood disorder and request more medication cocktails, showing little interest in talking therapy.

All these factors help to explain why the mood disorder model remains dominant, and some psychiatrists *never* diagnose a personality disorder. As shown by Zimmerman et al. [15] in a large clinical sample, PDs are highly prevalent but often missed. Of course it is also possible to misdiagnose a mood disorder as a PD, but that is less of an issue in the climate of contemporary psychiatry. Historically, the DSM system tried to encourage clinicians to think about personality by introducing multiaxial diagnosis. But Axis II was a failure, and it only succeeded in marginalizing the concept. In clinical reports, one often sees a statement that Axis II is "deferred," i.e., to be ignored. In contemporary psychiatry, the roots of psychopathology in personality are downplayed, while many aspects of life are medicalized and understood as epiphenomena of an abnormal mood.

It is often said that PDs cannot be diagnosed in the presence of depression, since abnormal mood distorts personality, and PD features can disappear once mood goes back to normal. While this is sometimes true, when patients are followed over several months, most personality disorder symptoms remain stable even when mood returns to baseline [16]. Yet this idea continues to be taught to students, discouraging them from taking the careful life history required for making a PD diagnosis. It serves as another rationale for ignoring personality disorders, given that patients usually come for treatment when mood is low.

Bipolarity and Personality Disorder

The introduction of lithium for the treatment of bipolar disorder was a heroic chapter in the history of psychiatry. But lithium is a powerful drug that should only be prescribed when definitely required. The introduction of anticonvulsant mood

stabilizers, however, made it more possible to consider treating outpatients with milder problems as suffering from variants of bipolar disorder.

The expansion of the bipolar diagnosis has been one of the most influential developments in modern psychiatry [17, 18]. The bipolar spectrum has been extended to patients with a wide range of disorders, including chronic depression, substance abuse, and children with behavior disorders, with the mood instability of BPD seen particularly as lying in a bipolar spectrum [19]. Akiskal [20] continues to see BPD as fictional but now views it as a form of bipolarity rather than depression. Needless to say, Akiskal views psychotherapy as misguided and favors pharmacological treatment for almost all these patients.

Other advocates of the spectrum have expanded the boundaries of classic bipolar disorders into all forms of mood instability, sometimes called "soft bipolarity" [21, 22]. While psychiatrists have few problems recognizing bipolar I, bipolar II disorder requires the presence of hypomanic episodes [23], i.e., 4 days of continuous abnormal mood associated with behavioral symptoms. Yet if one reads journal articles carefully, mood swings of any kind can lead to either a diagnosis of bipolar II or of "bipolar disorder, not elsewhere classified" [19].

The trajectory of this expansion could eliminate the diagnosis of BPD as well as most other PDs. These ideas have also been very influential. It is rare to see a patient with the classical features of BPD who has not been given a bipolar diagnosis by someone. The idea that mood swings, even when brief, are a sign of bipolarity has also gained currency among primary care physicians. Yet expansion of the spectrum has not been supported by controlled trials showing that patients with "soft bipolar" symptoms benefit from mood stabilizing medication [24] or that patients with PDs benefit consistently from their prescription [10]. Moreover, there is evidence that affective instability (AI) in BPD could be a unique phenotype and differs from classical hypomania [25]. When patients have AI, mood shifts by the hour, not by the week, and does not arise spontaneously but is strongly related to interpersonal events and stressors [26].

Reductionism and Medicalization

The decline of the concept of personality disorder is an incidental effect of a larger trend in psychiatry. While PDs, like other mental disorders, are associated with biological variations, they are too complex to fit a reductionistic neurobiological model. It does not make sense to reduce maladaptive life choices to neurochemistry. Once one conceptualizes a problem as a PD, one has to give serious consideration to psychosocial factors in etiology and treatment. In contrast, when one sees patients as suffering from depression or bipolarity, it is possible to consider them as equivalent to medical disorders. These diagnoses may also be perceived as reducing stigma.

Yet depression is defined so broadly these days that it describes all forms of human unhappiness [27]. The assumption seems to be that life should be happy, and that if isn't, you have a mental disorder. This perspective also fails to separate depression into melancholic cases in which medication is necessary and non-melancholic cases in which it may not be required [28]. In the same way, bipolarity medicalizes variations in personality traits and has come to be a code word, in both medical and common parlance, to describe people who are moody and difficult.

Contemporary psychiatry hopes to expand its triumphs in the golden years of psychopharmacology and has made a bet that neuroscience research will eventually solve the mystery of mental illness. Personality disorders are rejected because they remind people of the bad old days when psychoanalytic concepts dominated the field. The author of a prominent textbook on the history of psychiatry [29] referred to borderline personality as a concept that only Woody Allen would take seriously.

Yet the loss of a personality disorder construct could have serious consequences for patients. Focusing on depression avoids the assessment of life course, which is necessary to understand the complex impact of personality on psychopathology. Also, current evidence shows that drugs only palliate the symptoms of PD, which are better managed with specific forms of psychotherapy [30]. Mood is the hammer that makes everything look like a nail.

Future Prospects

While research on genetics, neuroimaging, or neurotransmitters has enriched psychiatric theory, these findings have not yet had any clinical application [31]. One reaction to the slow progress in the field is to assume that concepts we know something about, like variations in mood, can explain why patients suffer from complex behavioral symptoms.

Psychiatrists are physicians who have been trained to see the body as a machine. They know a good deal about chemistry and physiology but rarely have a strong background in psychology. Some physicians are uncomfortable with the complexity that social sciences bring to practice. They have been trained to reach firm conclusions after conducting differential diagnosis and to offer treatment that is targeted and specific. They are uncomfortable with complex interactions between multiple risk factors that determine psychopathology. They pay only lip service to the biopsychosocial approach [32], which remains a useful model for studying complexity.

If mood disorder advocates are right, the concept of personality disorder should be jettisoned and psychotherapy abandoned as a treatment. But if they are wrong, diagnosing almost every PD patient with a mood disorder will lead to incorrect and harmful treatment. Thus, the problem of the boundaries of mood and personality disorders is central to the identity of psychiatry and to its future.

References

1. Costa PT, Widiger TA, editors. Personality disorders and the five factor model of personality. 3rd ed. Washington, DC: American Psychological Association; 2012.
2. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, text revision. 5th ed. Washington, DC: American Psychiatric Press; 2013.
3. Lesse S. Masked depression–a diagnostic and therapeutic problem. Dis Nerv Syst. 1968;29: 169–73.
4. Shorter E. Before prozac. New York: Oxford University Press; 2009.
5. Akiskal HS, McKinney Jr WT. Depressive disorders: toward a unified hypothesis. Science. 1973;182:20–9.
6. Angst J, Merikangas K. The depressive spectrum: diagnostic classification and course. J Affect Disord. 1997;45:31–9.
7. Millon T. On the history and future study of personality and its disorders. Annu Rev Clin Psychol. 2012;8:1–19.
8. Akiskal HS, Chen SE, Davis GC. Borderline: an adjective in search of a noun. J Clin Psychiatry. 1985;46:41–8.
9. Gunderson JG, Phillips KA. A current view of the interface between borderline personality disorder and depression. Am J Psychiatry. 1991;148:967–75.
10. Stoffers J, Völlm BA, Rücke G, Timmer A, Huband N, Lieb K. Pharmacological interventions for borderline personality disorder. Cochrane Database Syst Rev. 2010;(6):CD005653. doi:10.1002/14651858.CD005653.pub2.
11. Carlat D. Unhinged. New York: Free Press; 2010.
12. Insel TR, Quirion R. Psychiatry as a clinical neuroscience discipline. JAMA. 2002;294: 2221–4.
13. Mojtabai R, Olfson M. National trends in psychotherapy by office-based psychiatrists. Arch Gen Psychiatry. 2008;65:962–70.
14. Gunderson JG, Stout RL, McGlashan TH, Shea MT, Morey LC, Grilo CM, et al. Ten-year course of borderline personality disorder: psychopathology and function from the Collaborative Longitudinal Personality Disorders Study. Arch Gen Psychiatry. 2011;68:827–37.
15. Zimmerman M, Rothschild L, Chelminski I. The prevalence of DSM-IV personality disorders in psychiatric outpatients. Am J Psychiatry. 2005;162:1911–8.
16. Lopez-Castroman J, Galfalvy H, Currier D, Stanley B, Mann JJ, Oquendo MA. Personality disorder assessments in acute depressive episodes: stability at follow-up. J Nerv Ment Dis. 2012;200:526–30.
17. Angst J, Gamma A. A new bipolar spectrum concept: a brief review. Bipolar Disord. 2002; 4:11–4.
18. Akiskal HS. The bipolar spectrum–the shaping of a new paradigm in psychiatry. Curr Psychiatry Rep. 2002;4:1–3.
19. Paris J. The bipolar spectrum: diagnosis or Fad? New York: Routledge; 2012.
20. Akiskal HS. Demystifying borderline personality: critique of the concept and unorthodox reflections on its natural kinship with the bipolar spectrum. Acta Psychiatr Scand. 2004; 110:401–7.
21. Ghaemi SN, Ko JY, Goodwin FK. "Cade's disease" and beyond: misdiagnosis, antidepressant use, and a proposed definition for bipolar spectrum disorder. Can J Psychiatry. 2002;47: 125–34.
22. Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RM, Petukhova M, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2007;64:543–52.
23. Parker G, editor. Bipolar-II disorder. Modeling, measuring and managing. 2nd ed. Cambridge: Cambridge University Press; 2012.
24. Patten S, Paris J. The bipolar spectrum–a bridge too far? Can J Psychiatry. 2008;53:762–8.

25. Koenigsberg H. Affective instability: toward an integration of neuroscience and psychological perspectives. J Pers Disord. 2010;24:60–82.
26. Russell J, Moskowitz D, Sookman D, Paris J. Affective instability in patients with borderline personality disorder. J Abnorm Psychol. 2007;116:578–88.
27. Horwitz AV, Wakefield JC. The loss of sadness: how psychiatry transformed normal sorrow into depressive disorder. New York: Oxford University Press; 2007.
28. Parker G. Beyond major depression. Psychol Med. 2005;35:467–74.
29. Shorter E. A history of psychiatry. New York: Wiley; 1997.
30. Paris J. Effectiveness of differing psychotherapy approaches in the treatment of borderline personality disorder. Curr Psychiatry Rep. 2010;12:56–60.
31. Hyman SE. The diagnosis of mental disorders: the problem of reification. Annu Rev Clin Psychol. 2010;6:155–79.
32. Engel GL. The clinical application of the biopsychosocial model. Am J Psychiatry. 1980; 137:535–44.

Part II
Defining Territories: Diagnostic Confusion and Comorbidity

Chapter 2
Depressive Disorders in Borderline Personality Disorder: Phenomenology and Biological Markers

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Introduction

The relationship between major depressive disorder (MDD) and borderline personality disorder (BPD) has remained controversial for over 25 years and continues to be the topic of numerous biological, phenomenological, and longitudinal studies. One of the fundamental questions that persist is whether BPD is a distinct disorder from MDD, and, if so, why there is such a high comorbidity between the two disorders. Several comprehensive reviews [1–3] offered multiple, and often contradictory, perspectives that included: (1) BPD is an atypical expression of MDD, (2) BPD is a distinct disorder and predisposes affected individuals to MDD, (3) BPD and MDD are independent illnesses and unrelated, (4) BPD and MDD have overlapping nonspecific sources, and (5) BPD and MDD share etiologic features and each

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can contribute to the development of the other. Theories #1–4 were debated by Gunderson and Elliott [1] and Gunderson and Phillips [2], with the conclusion that MDD and BPD frequently coexist because of the high prevalence of each, but that they are two distinct disorders and otherwise unrelated. In 1999, Koenigsberg and colleagues, using data collected over the previous 8 years, including biological and early neuroimaging studies, reached an alternative conclusion that MDD and BPD coexist because they share common biological features and each can foster the development of the other [3]. This chapter reexamines the relationship between MDD and BPD in light of an additional fourteen years of data since the Koenigsberg review by directly comparing phenotypic expressions and putative genotypes and neuroimaging and biological endophenotypes for the two disorders.

We propose that BPD is a disorder of emotional dysregulation, with additional components of impulsivity and interpersonal sensitivity, distinct from MDD. While both disorders involve mood alterations, the key distinguishing factor for BPD is the sensitivity to affective shifts which are transient and reactive in comparison to the sustained mood problems seen in MDD. This affective instability in BPD is fundamentally distinct from the mood disturbance in MDD. We further posit that any overlapping symptomatology between these disorders may stem from an overlap in underlying biology, but that the disorders have specific features that distinguish each from the other. The biology that makes individuals vulnerable to each disorder is as yet only beginning to be understood. Abnormalities in the neural circuitry underlying emotion regulation appear common to both disorders, as evidenced by the overlap in neuroimaging findings. While most family studies suggest that BPD and MDD do not run together in families, the minimal data available to date for putative genotypes of BPD demonstrates significant overlap with MDD and other psychiatric disorders. Lastly, we agree in part with Koenigsberg's hypothesis about each disorder's effect on the development of the other, but consistent with more recent findings [4], we believe that when the two diseases coexist, BPD tends to dominate the clinical picture.

Overview: Phenotypes, Endophenotypes, and Genotypes

Because of the complex genetics of psychiatric disorders [5], any hopes of uncovering Mendelian inheritance patterns for them have, for the most part, been abandoned in favor of models incorporating genetics, epigenetics [6], environmental factors [7], and gene–environment interactions [8]. It has further become apparent that, rather than conforming to a one gene one illness model, the risk of developing psychopathology is conveyed by multiple genes of small effect [9]. In order to derive meaningful information about the genotypes underlying mental illnesses, researchers have increasingly focused their attention on intermediate phenotypes, traits, or symptoms that are parts of the full syndromal phenotype, and endophenotypes, defined in one recent review as "measurable components unseen by the unaided eye along the pathway between disease and distal genotype" [10]. [Although some authors [11] use

endophenotype and intermediate phenotype interchangeably, we will use them to describe distinct entities, as defined above.] To be considered an endophenotype, a feature should be measurable, reproducible, and state-independent. The feature should also occur at a greater rate in affected probands than in unaffected family members or in the general population and at a greater rate in unaffected family members than in the general population [12].

Phenotype Comparison

Apart from affective symptomatology, the DSM-IV descriptions of BPD and MDD reveal minimal phenomenologic overlap. Some authors [13] have cast doubt on the diagnostic integrity of BPD. However, an examination of the BPD and MDD phenotypes provides more support for the diagnostic integrity of BPD than it does for MDD, as demonstrated by factor analyses of the diagnostic criteria for each disorder.

An early factor analysis, and subsequent replication study, of symptoms in large samples of BPD patients revealed three factors: disturbed relatedness (unstable relationships, identity disturbance, and chronic emptiness), behavioral dysregulation (impulsivity, suicidality/self-mutilatory behavior), and affective dysregulation (affective instability, inappropriate anger, and efforts to avoid abandonment) [14, 15]. A number of recent studies, however, have shown that the factors correlate so highly with one another (with correlation coefficients of 0.92–0.98) that the factor analyses actually support an overarching BPD construct [16–18].

In contrast, factor analyses of MDD symptoms have suggested that MDD often is composed of a varied set of underlying symptom clusters. Using the Zung Self-rating Depression Scale, for example, core depression, anxiety, and somatic and cognitive factors were identified [19], while an analysis using the Hamilton Depression Scale revealed depressive mood, somatic anxiety, psychic anxiety, and anorexia factors [20]. Thus, while factor analyses of MDD do demonstrate a core depression factor, the MDD syndrome appears to carry within it additional other factors that vary in their presentation in affected individuals, which suggest that the MDD syndrome may be a heterogeneous construct.

Intermediate Phenotypes in MDD and BPD

An excellent review by Hasler et al. [21] describes intermediate phenotypes for MDD, including negative mood bias, impaired reward function, impaired learning and memory, appetite and diurnal variation change, psychomotor slowing, and increased stress sensitivity. Overlap with BPD is limited to negative mood bias and stress sensitivity. However, even these factors differ in their presentation in BPD and in MDD. In BPD, the negative mood bias is less sustained and more labile than in MDD, and the stress sensitivity in BPD is confined to the interpersonal sphere,

whereas in MDD, it appears to have broader scope. Proposed intermediate phenotypes unique to BPD include impulsive aggression [22] and, possibly, interpersonal sensitivity, particularly fears of interpersonal rejection [23].

Depressed Mood in BPD: A Distinct Phenotype?

A high percentage of individuals with BPD struggle with depressed mood, and the estimated prevalence of MDD in BPD ranges from 37.4 to 70.9 % [24, 25]. Often, individuals with BPD without MDD score comparably on self-rated depression scales as individuals with BPD and MDD and individuals with MDD without BPD [26]. However, numerous reports suggest that the subjective quality of depressive symptoms in BPD differs from that in MDD, with pronounced ingredients of emptiness, loneliness [27], and fears of abandonment [28]. Similarly, Siever et al. [29] noted that MDD episodes in BPD are more reactive than melancholic forms of MDD [29]. In a recent study [30] comparing features of mood phenomenology in BPD and MDD, BPD subjects demonstrated higher scores on every domain and subdomain of the Mood Spectrum Self-Report, with the greatest discrepancy noted on the subscales of cognition and mood. (Cognitive symptoms included aspects of hypercriticism, guilt, and suicidal ideation.) These findings, coupled with the differential pharmacological response to antidepressants, with a more refractory response in BPD [31], suggest that depressive mood in BPD may reflect a different phenotype from that of MDD.

Longitudinal Course of MDD and BPD

Long-term outcome studies in MDD and BPD seem to challenge the traditional Axis I/Axis II dichotomy, in which mood disorders are widely thought of as episodic and treatable, whereas personality disorders are considered lifelong and treatment refractory. Many cases of MDD assume a chronic course, with long-term morbidity and substantial inter-episode symptomatology [32, 33], whereas multiyear follow-ups of BPD samples have found that most subjects eventually stop meeting threshold criteria for the disorder [34, 35]. However, there appear to be a core subset of BPD symptoms, especially in the affective and interpersonal realms, that persist even after the more dramatic, impulsive, or demanding behaviors have subsided [36], as well as a subset of BPD patients who fail to remit and continue to show poor judgment and high treatment utilization [37]. Of note, in a longitudinal study that directly compared individuals with BPD (or other personality disorders) and those with MDD and no personality disorders, BPD at study entry was a far more robust predictor of sustained functional impairment than was MDD [38]. Similarly, in a longitudinal study of BPD and functioning, remission of BPD was slower than for MDD [39].

The literature on BPD–MDD comorbidity suggests that the presence of comorbid BPD complicates the course of MDD, with an earlier onset of depression, a higher rate of other comorbidity on Axes I and II, a greater history of conduct disorder, and elevated levels of anger/hostility [40]. In the presence of comorbid BPD, the course of MDD is more severe, with an increased likelihood of relapse and treatment efforts being less successful [4, 38, 41].

Gunderson and colleagues [4] contend that when the two disorders coexist, BPD generally is the dominant psychopathology and that MDD may be considered an epiphenomenon. They further propose the existence of an underlying affective instability phenotype comprised of anger, lability, emptiness, self-destructive behavior, and brief psychotic symptomatology that could potentiate MDD exacerbations [4].

Genotypes

Genetic Vulnerability

As with many other illnesses, the etiology of both BPD and MDD is likely to be an interaction of heritable vulnerability with environmental factors that combine to bring about the full presentation of disease. Do similar heritable vulnerabilities place individuals at risk for both disorders?

For BPD, according to the common pathway model, both genetic and environmental factors contribute to affective instability, identity problems, negative relationships, and self-harm (four main features of BPD) through a single latent BPD factor. This factor was found to have a heritability of 51 % by Distel et al. [42] and a 60 % heritability in a more recent study [43]. The genes that influence BPD characteristics may also increase the chance of exposure to traumatic life events such as sexual violence, divorce, and job loss [44].

Family/Twin Studies

Family and twin studies have been investigating the genetic vulnerabilities and heritability seen in BPD and MDD. Family studies have looked at the relationship between genetic and environmental factors and their interactive effects on the disorders. Gunderson et al. [45] conducted a comprehensive family study of BPD and its four sectors of psychopathology (affective, interpersonal, behavioral, and cognitive) in order to gain a better understanding of familial aggregation in BPD. The prevalence of BPD in relatives of probands without BPD was 4.9 % and was 14.1 % in relatives of probands with BPD. In addition, analyses found that all four sectors of psychopathology showed significant levels of familial aggregation and that the relationship between the four sectors can be best explained by a common pathway model. This supports previous studies that suggest a common pathway model for BPD [42, 46].

Multiple studies have examined the prevalence of MDD in BPD probands, yielding estimates between 4.6 and 31 % [47]. In an early family study of BPD, familial relation of affective instability and impulsivity rather than affective disorders was noted, and MDD comorbidity in the personality-disordered probands explained greater rates of depressive disorder in relatives [48]. This last finding highlighted the need for family studies examining BPD individuals with no history of MDD. Three such studies found diminished risk of affective disorder in relatives of pure BPD probands versus relatives of individuals with comorbid BPD–MDD [49–51], which suggests independent familial risk for the two disorders. However, the possibility of familial coaggregation of MDD and BPD was explored by Riso et al. [52], who found evidence for a common etiological factor.

Family studies can indirectly reflect heritability; however, only twin studies provide definitive evidence for genetic heritability. While limited data from twin studies is available for BPD, two recent studies examined the heritability of MDD and BPD together. In a multivariate study of 2,894 members of the Norwegian Institute of Public Health Twin Panel, Kenneth et al. [53] found evidence of a broad genetic risk factor for personality disorder pathology, suggested to be negative emotionality, as well as a specific genetic risk factor for borderline and antisocial PDs which may be impulsive aggression. Another twin study examining 92 monozygotic twins and 129 dizygotic twins showed that BPD was substantially heritable, with 69 % of the variance in BPD accounted for by genetic factors [54]. Lastly, the heritability of BPD characteristics can be seen in children as young as 12 years old [55]. Twin studies examining both MDD and BPD together yield contrasting results. Kendler et al. [46] suggest partially different genetic etiological factors, while Reichborn-Kjennerud et al. [56] found significant overlap between genetic liability factors for MDD and BPD and noted the genetic correlation between MDD and BPD to be $r = 0.56$.

For unipolar depression, the heritability estimate, based on four community samples and two clinical samples, is 33–42 % [57, 58]. A more heritable phenotype of MDD has been identified, with features including younger age of onset and multiple episodes [59].

Taken together, there is a growing database with respect to the shared versus distinct heritable risk of MDD and BPD that suggests overlap in genetic etiological factors. Additional twin studies examining both disorders in one data set are needed to clarify the extent of the overlap.

Genetic Studies

Research into the specific genes involved in BPD is at a very early stage with findings focused on genes of the serotonin (5-HT) system including serotonin transporter (5-HTT), tryptophan hydroxylase (TPH), monoamine oxidase A (MAO-A), 5-HT2c and 5-HT2a, and dopaminergic systems.

A recent case-control study showed a significant association between the serotonin transporter (5-HTT) gene and BPD, with higher frequencies of 10-repeat of the VNTR marker and the S-10 haplotype and fewer 12-repeat and LA-12 haplotype in BPD patients compared with healthy controls [60]. This result is consistent with the findings of a genetic association between the low-expressing short allele and aggressive behavior [61], as well as with NEO ratings of neuroticism, which is characterized by negative emotionality, including anxiety, depression, vulnerability, and hostility [62]. Furthermore, a study of gene variants of the 5-HTT gene found that carriers of two short alleles of the 5-HTTLPR polymorphism reported more symptoms of anxiety, depression, and obsessive-compulsive behaviors [63]. A simultaneous case-control study of the same gene in BPD, however, was unable to replicate these findings [64].

TPH, the rate-limiting enzyme in 5-HT biosynthesis, has two isoforms, TPH-1 and TPH-2. In a recent case-control study, in both BPD patients and controls, six single nucleotide polymorphisms (SNPs) were found at significant linkage disequilibrium across the TPH-1 gene [65]. Using haplotype analysis, configurations between the gene promoter and intron 3 were associated with the BPD group, suggesting TPH-1 gene involvement in BPD suicidal women [65]. Furthermore, certain polymorphisms in TPH-1 may increase risk for developing BPD, in conjunction with environmental factors such as childhood abuse [66]. Another study noted increased frequency of a TPH-1 haplotype in BPD subjects who exhibited poor scores on the Iowa Gambling Task compared to BPD subjects with normal scores [67]. An association between the TPH-1 A218 polymorphism and BPD diagnosis has also been found [68]. The rs2171363T allele and T-containing genotypes of TPH-2, a brain-specific isoform of TPH, have been associated with BPD [69], and the presence of a previously identified TPH-2 "risk" haplotype comprised of 15 single nucleotide polymorphisms spanning a 106-Kb TPH-2 region was significantly higher in individuals with BPD compared to healthy controls, further implicating a link between this gene and BPD [70].

Single study findings note an association with BPD diagnosis and genes for MAO-A, a key regulator of serotonin metabolism [71] and 5-HT2c [69]. However, 5-HT2a gene variants are associated with personality traits but not with BPD diagnosis [72]. Interestingly, BPD subjects carrying the HTR1B A-161 allele were found to also carry more of the brain-derived neurotrophic factor (BDNF) 196A allele compared to healthy controls [73]. While these preliminary studies of specific genes implicated in BPD are promising and support the presence of a serotonergic abnormality in this disorder, they will require replication for any definitive conclusions to be drawn.

Lately, there is growing speculation that other catecholamine systems, including dopamine, may play a role in the behavioral manifestations of BPD, although data on this is limited. Joyce et al. [74] found that the 9-repeat allele of the dopamine active transporter 1 gene is associated with angry-impulsive personality traits, which may increase the risk of BPD. Wagner et al. [75] reported a positive association between serious life events such as child abuse and impulsive aggression and

that the catechol-O-methyltransferase (COMT) Val(158)Val genotype has a modulating effect on the relationship.

Recently, Dammann et al. [76] studied DNA methylation of some of the previously mentioned neuropsychiatric genes (i.e., 5-HTT, TPH-1, MAO-A). Epigenetic alterations are trademarks of altered gene expression, which may contribute to psychiatric illnesses such as BPD; these alterations are correlated with DNA methylation. A comparison of DNA methylation of genes in individuals with BPD and healthy controls showed a significant average increased methylation (1.7 %) in the genes of individuals with BPD [76]. This supports the notion that abnormal epigenetic regulation may be involved in the etiology of BPD.

There is almost complete overlap in candidate genes for MDD with BPD. Several studies have reported positive associations between 5-HTT gene variants and MDD [77–79], but many more have failed to show any association [80–83]. Variants of the 5-HTT gene have been associated with structural and functional differences in key brain regions for MDD, including more pronounced amygdala activation in response to threatening and negative emotional stimuli [32, 84], alterations of the amygdala–cingulate feedback circuit [85], and, when coupled with adverse events, an increased level of depressive symptoms [8].

Because the 5-HTT gene is directly involved in selective 5-HT reuptake inhibition, it was hoped that genetic variations at the relevant alleles would shed light on variations in antidepressant treatment response. However, the largest study to date that has examined 5-HTT and H-HT2A receptor genes, The Sequenced Treatment Alternatives to Relieve Depression (STAR*D), did not find genetic predictors of treatment response for 5-HTT, but found an association with a marker on the 5-HT2A receptor [86].

Variants of TPH-2 have been positively associated with MDD [87] and multiple studies have confirmed an association with suicide [88–90]. Similar to BPD, examinations of possible correlations of MDD with variants of the 5-HT2A gene have yielded inconsistent results.

There exists a polymorphic variation in the X-linked MAO-A gene that influences its expression which has been associated with sex-specific variation in 5-HT(1A) receptor expression [91], increased risk for major depressive disorder in females [92], and antidepressant treatment response in women [93].

The BDNF gene has gained interest, given its role in neurogenesis [94] and the discovery of an association between the Val66Met polymorphism and bipolar disorder [95]. However, findings in unipolar disorder have been negative to date [96, 97].

In summary, there exists substantial overlap in the genetic building blocks studied in MDD and BPD. Overlapping findings in candidate genes (e.g., 5-HTT and TPH) likely reflect the two disorders' shared substrate of altered emotional information processing, but they may also be manifestations of the early stages of this line of inquiry. The field awaits implementation of more sophisticated methodology such as linkage studies and whole-genome explorations to further clarify genetic similarities and differences between the two disorders.

Biological Markers for MDD and BPD

Putative biological endophenotypes for MDD outlined in the Hasler review [21] include hypothalamic-pituitary-adrenal axis (HPA) dysfunction, REM sleep abnormalities, neuroimaging findings of increased amygdala activity, decreased subgenual prefrontal cortex activity, left anterior cingulate and hippocampal volume reduction, and reduced 5-HT1A receptor binding. Additionally, alterations in monoamines including 5-HT, dopamine, and norepinephrine have been described. Many of the same systems have been examined in BPD.

Specific Biological Endophenotypes for MDD and Their Overlap with BPD

In the Koenigsberg review of MDD and BPD [3], the following biological parameters were compared: HPA axis and dexamethasone suppression test, thyroid-stimulating hormone (TSH) and thyrotropin-releasing hormone (TRH) function, platelet monoamine oxidase activity, platelet alpha$_2$-adrenergic receptor binding, growth hormone response to the alpha$_2$ agonist clonidine, REM sleep, emotional responses to cholinomimetics (e.g., physostigmine), and serotonergic responsivity. While most of the above parameters showed marked differences between the two disorders, MDD and BPD did share heightened reactivity of the cholinergic system and decreased 5-HT responsivity. However, the blunted prolactin response to fenfluramine was more closely associated with signs and symptoms of impulsive aggression, in both populations, than with diagnosis [98, 99]. Following are data on biological parameters from 1999 to 2012, focusing on dimensions identified in the Hasler MDD endophenotype review including HPA axis and corticotrophin-releasing hormone (CRH) dysfunction, impaired sleep architecture, brain imaging abnormalities, and diminished 5-HT function. Data for MDD and BPD will be compared for each entity.

Neuroendocrine: HPA Axis/CRH

In MDD, there exists extensive evidence of HPA axis and CRH system dysfunction. The dexamethasone suppression test and CRH stimulation test have an 80 % sensitivity in MDD [100] and are believed to be state-independent and to demonstrate familial association and cosegregation [101]. Similarly, it is widely accepted that cortisol has a role in MDD, including the somatic signs and symptoms of the illness, such as alterations in sleep, appetite, and libido [102].

Koenigsberg and colleagues [3] compared HPA axis and CRH dysfunction data through 1999 for MDD and BPD and concluded that findings in the two disorders differed. Studies since 1999 have continued to support this viewpoint. In contrast to findings of cortisol nonsuppression in MDD, several investigators [103–106] have found enhanced cortisol suppression in individuals with BPD and comorbid posttraumatic stress disorder (PTSD), though they have concluded that the response was due to the comorbid PTSD and not the BPD diagnosis itself. However, a recent brief report [107], using a 0.25 mg dexamethasone suppression test dose, found enhanced cortisol suppression in individuals with BPD without PTSD, suggesting that increased feedback inhibition of the HPA axis may exist in BPD that is not accounted for by PTSD. Walter and colleagues [108], in a small pilot study, noted a delayed cortisol response after psychosocial stress in BPD compared to normal control subjects; the BPD subjects were not formally assessed for MDD, though they did exhibit more depressive symptoms. Minimal work on TRH and BPD has been published since 1999.

De la Fuente and colleagues [109], strong proponents of the position that MDD and BPD are distinct disorders that do not share a common biological substrate, noted less TRH stimulation test blunting in BPD than MDD.

Sleep Studies

Aspects of REM sleep including REM latency and REM density have been associated with state independence in MDD [110] and have been found in probands' first-degree relatives [111]. Antidepressant medications result in inhibition of REM sleep [112], and candidate genes such as the CREB gene that are involved in the regulation of REM sleep have been proposed for MDD [113].

In BPD, there exist multiple studies of REM sleep and sleep architecture in BPD patients without Axis I comorbidities, which found that BPD subjects had shorter sleep time and lower sleep efficiency than healthy controls [114]. In particular, sleep fragmentation, elevated REM sleep pressure, lengthened slow-wave sleep, and disturbed dreaming may be associated with different BPD characteristics such as affective dysregulation, impulsivity, and dissociative tendencies [115].

A review of sleep disturbance studies in BPD concluded that previous literature shows disturbed EEG patterns in both BPD and MDD [116]. However, few studies have accounted for BPD with Axis I comorbidities, and those that did concluded that sleep-EEG abnormalities were linked to the comorbid MDD [117, 118]. One of the few studies to compare MDD and BPD directly found differing patterns of sleep architecture and sleep continuity, including differences in sleep-EEG patterns of continuity, total sleep time, sleep onset latency, and percentage of wakefulness (Table 2.1). Moreover, BPD subjects had more stage 2 sleep, longer REM sleep duration, and less slow-wave sleep than individuals with MDD [119]. These data point to differing sleep profiles between the two disorders, implying dissimilar biological substrates in this domain.

Table 2.1 Comparison of neuroendocrine and sleep study findings

	MDD	BPD
HPA axis	Cortisol non-suppression	↑ Cortisol suppression in BPD/PTSD and BPD
Thyrotropin-releasing hormone		BPD blunting > MDD
Sleep studies	Differences from BPD in patterns of sleep architecture	↑ Stage 2 sleep
	Sleep continuity	↑ REM sleep duration
	Total sleep time	↑ Slow-wave sleep
	Sleep onset latency	
	% of wakefulness	

Neuroimaging

Over the past decade, much of the literature concerning the relationship between MDD and BPD has shifted from endocrine parameters to direct visualization of brain structure and function through neuroimaging. While both disorders have been studied using structural and functional MRI and PET scanning, to date, there have been no neuroimaging studies directly comparing MDD and BPD. Comparing individual findings in the two disorders is compromised by technical differences between the pertinent studies and by the fact that studies of MDD do not report on BPD comorbidity. (Studies of BPD tend to include subjects with a history of depressive episodes, as this is true of most individuals with BPD, but most exclude patients with a current major depressive episode (MDE).) Nonetheless, we review current imaging findings for both disorders, recognizing that the ability to compare findings from one body of literature to the other is limited.

Neural systems relevant to MDD include those that involve emotion regulation, emotion processing, and reward seeking [120]. In a review of new developments on MDD, Kupfer et al. [120] found that neuroimaging studies showed evidence that these systems are dysfunctional in the disorder. Hasler et al. [21] proposed several brain abnormalities as putative endophenotypes for the disorder, including increased amygdala activity, decreased subgenual prefrontal cortex (PFC) activity, left anterior cingulate cortex (ACC) volume reduction, and hippocampal reduction. Each of these will be discussed separately and compared to findings in BPD.

Increased Amygdala Activity

Structural imaging studies of amygdala volume in MDD are inconsistent, with some reporting increased amygdala size [121], others noting decreased size [21], and others showing no difference from normal controls [122, 123]. In BPD, as in MDD, volumetric studies have yielded discrepant results, with reports of volume

reduction [124–128], perhaps reflecting excitotoxicity with volume loss, alongside studies citing no volume differences [129–131]. Taken together, MDD and BPD structural imaging studies do not converge on a consistent finding regarding amygdala volume.

The amygdala has been viewed as the subcortical structure from which fear and perhaps anger may emerge. Amygdala activity is typically studied after exposure to a fear-inducing stimulus. In MDD, however, amygdala hyperactivity has been consistently reported [132] even at rest, perhaps due to internally generated thoughts of anxiety or sadness [133]. Similarly, increased amygdala activity is found in MDD during REM sleep, when conscious processing of stressors is not occurring. Subjects with MDD show exaggerated response to increasingly sad faces in the left amygdala and other areas that process facial emotion compared to healthy controls [134]. There is less clarity regarding amygdala response to positive stimuli [134, 135].

While increased amygdala activity in response to negative stimuli has been consistently reported in MDD, there are contradictory findings regarding amygdala activity in BPD. fMRI studies in BPD do not show increased amygdala activity when at rest as in MDD. However, increased amygdala activity is shown in BPD in response to specific types of stimulus [136] (e.g., "unresolved" life events), emotional faces [137], scenes of threat and suffering [138], positive and negative emotional pictures [139], and scripts [140]. Hazlett and colleagues [139] also reported an increase in amygdala activity to emotional stimuli. Contrary to earlier studies, however, Goodman et al. (in press) found baseline amygdala activity (at rest) to be higher in BPD subjects when compared to healthy controls. Similar amygdala hyperactivity is seen in impulsive aggressive personality-disordered subjects in response to emotional faces [141]. Furthermore, prolonged amygdala activity is seen when subjects are exposed to negative stimuli such as electrodermal stimulation [142]. These findings suggest overlap in amygdala hyperactivity in both disorders, but with differences at rest and potential variation according to type of emotional stimuli. In addition, BPD patients seem to show particularly robust responses to other emotions, including anger [143]. However, contrary to these previous findings, a meta-analysis of the neural correlates of negative emotionality in BPD found that BPD subjects showed less amygdala activity than control subjects in response to negative emotional stimuli [144] (Table 2.2).

Anterior ACC

Numerous studies in MDD have noted volume reductions in subgenual and pregenual ACC. The subgenual ACC is involved in the subjective experiencing of [123] and is viewed as a critical structure in the pathogenesis of MDD. The left subgenual ACC is reported to have 20–40 % gray matter volume reductions [145], but despite these volumetric decreases, some studies suggest that there is hyperactivity of the remaining subgenual tissue, which decreases to normal with effective antidepressant treatment [133] and is the target of deep brain stimulation [146].

Table 2.2 Comparison of neuroimaging studies of the amygdala

	MDD	BPD
Amygdala volume	Inconsistent findings	Inconsistent findings
		↓ Volume[a]
Amygdala activity	↑ Activity[b]	↑ Activity

[a]Recent meta-analyses
[b]Including at rest

However, a meta-analysis of neuroimaging data on altered emotion and cognition in MDD reported hypoactivity in subgenual tissue when not at rest [147]. Additionally, subgenual measures, such as decreased pretreatment responsivity to negative words, have been associated with treatment outcome in cognitive behavior therapy [148]. In the pregenual ACC, findings regarding the effect of treatment have been less consistent [149].

The ACC has also been a region of interest in BPD. Evidence suggests decreased gray matter volume and increased white matter volume in rostral [150] and subgenual [151] cingulate in individuals with BPD but no current MDD compared to healthy controls. Functional imaging studies in BPD have tended to show decreased activation of the ACC in response to provocation. Schmahl and colleagues [136] noted in 12 BPD subjects (one with current MDE and 11 with history of MDD) diminished activation of the perigenual ACC with induction of pain. Several other functional imaging studies in BPD also show decreased activation of the ACC in response to provocation [143, 152, 153]. Silbersweig and colleagues [154], using a behavioral inhibition task during the induction of negative emotion with fMRI, demonstrated decreased activation in the subgenual ACC and orbitofrontal cortex (OFC), with increases in amygdala activity, prompting their group and another [148] to propose that BPD sits at the "intersection of cognition and emotion" and ponder whether this constellation of impaired regions is specific to BPD.

Pharmacologic probes have also shown decreased metabolic activity in the ACC and OFC in response to the serotonergic challenge in BPD patients with impulsive aggression [155, 156] and with affective instability [157] compared to healthy controls. Decreased coupling of resting metabolism between the OFC and ventral ACC has been reported by our group [130]. A recent case study of a patient with schizencephaly [158] resulting in a primary ACC and secondary OFC lesion, who prominently manifested symptoms of BPD, supports the notion of important interconnections between these two brain regions in the development of BPD, but not MDD.

Taken together, these studies suggest similar decreases in ACC volume in MDD and BPD. By contrast, while there appears to be an overlap in the anatomic region of aberrant processing (ACC and adjacent OFC) between MDD and BPD, differences exist in the functional responses of these brain regions: In MDD they are generally hyperreactive, only when corrected for volume loss, while in BPD they appear to be under-responsive.

Table 2.3 Comparison of neuroimaging studies of the ACC and hippocampus

	MDD	BPD
Anterior cingulate cortex (ACC) volume and activity	↓ Volume subgenual ACC[a]	↓ Subgenual volume in BPD/no MDD
	Target of deep brain stimulation	↓ Activation of ACC to provocation
	Others report ↓ activity	
Hippocampal volume	↓ Volume in most studies but not all	↓ Volume[b]

[a]Hyperactivity ↓ until normal with antidepressant treatment
[b]Associated with trauma/abuse

Hippocampus

Decreased hippocampal volume has been reported in MDD in most, but not all, studies, with 8–19 % difference from normal controls [21, 122, 159, 160]; for a meta-analysis of these findings, see Videbech and Ravnkilde [161]. A recent meta-analysis by Kempton et al. [162] also reports decreased hippocampal volume in MDD. Volume loss appears to be inversely related to time spent depressed [163]. However, hippocampal volume loss is also found in other disorders, such as PTSD and schizophrenia.

In BPD, hippocampal volume loss has been reported in some [164–166] studies, but appears to be associated with extent of trauma [167] and abuse history [129], reflecting comorbidities with PTSD rather than specificity to BPD itself [168]. An exception to this, however, is a recent study [166] that found hippocampal volume reductions in BPD to be inversely correlated with aggressive but not impulsive symptomatology. Recent meta-analyses also support previous findings of hippocampal volume decrease in BPD [128, 168] (Table 2.3).

Other Brain Regions

Other neuroimaging findings not cited by the Hasler review but implicated in MDD include increased metabolism in the posterior cingulate [133], a region believed to function as a sensory association cortex where processing of affective salience occurs, and decreased cerebral blood flow and metabolism in the dorsal medial PFC, whose impairment affects the ability to modulate emotional responses. The ventrolateral PFC, lateral orbital regions, and insula are reported to show increased metabolism in MDD; however, these findings appear to be state dependent and to improve with treatment [149].

In BPD, similar findings of posterior cingulate activation were noted by New and colleagues [156] in their 5-HT challenge study. However, other findings include volume loss [152] in the region and diminished uptake with PET scanning in BPD females with dissociation and history of childhood sexual trauma, phenomena which complicate the clinical picture and obscure the direct contribution of BPD symptomatology to the posterior cingulate findings [169].

Table 2.4 Comparison of neuroimaging studies in 5-HT function

	MDD	BPD
5-HT function	Peripheral, postmortem, imaging, and antidepressant treatment studies provide evidence for ↓ 5-HT function (5-HT1A receptor and 5-HTT receptors are of particular interest)	PET study of BPD showed ↓ 5-HT synthesis ↑ Binding in hippocampus ↓ Availability of 5-HT transporter in the ACC

Diminished Serotonin Function

There exists considerable evidence from multiple perspectives, including peripheral, postmortem, imaging, and antidepressant treatment studies, of diminished 5-HT function in MDD. Defects in the 5-HT1A receptor [88] and 5-HTT [170] have been particular sites of inquiry.

The mechanism of the serotonergic abnormality in BPD has recently been examined with molecular neuroimaging studies. A PET study of 5-HT synthesis showed lower synthesis in men with BPD compared to controls in the medial frontal gyrus, ACC, superior temporal gyrus, and corpus striatum; women with BPD had lower 5-HT synthesis compared to controls in the right ACC and superior temporal gyrus [171]. Increased binding was found in the hippocampus in impulsive BPD females independent of mood [172]. More recently, we employed the 5-HTT PET radiotracer [11C] McN 5652 to show reduced availability of 5-HTT in the ACC of personality-disordered individuals with impulsive aggression compared to healthy controls, suggesting reduced serotonergic innervation in this brain region [173]. Interestingly, evidence shows an association between a particular haplotype in the 5-HTT gene (10-repeat of the VNTR intronic marker and the short form of a promoter polymorphism) and BPD, which lends further support to the notion that genetic differences in 5-HTT may play a role in the etiology of the disorder [72]. Impulsive aggressive subjects with BPD are being studied in our lab with PET to determine whether reduced numbers of 5-HTT as indexed by [11 C] DASB-specific binding exist in the cingulate cortex.

Taken together, the published evidence regarding 5-HT suggests that there exist similarities between MDD and BPD, with a serotonergic abnormality that may underlie the impulsive aggressive symptoms of BPD and may be related to specific genetic risk factors, but the precise molecular nature of this abnormality is not yet clear for either disorder (Table 2.4).

Conclusions

We have examined data from the last 14 years pertinent to the relationship of MDD and BPD, including comparisons between the two disorders' phenotypes and putative endophenotypes and genotypes, focusing heavily on neuroimaging findings.

We assert that BPD and MDD are distinct disorders with overlapping biological processes pertaining to emotional regulatory functions. While both disorders share affective symptomatology, the disturbances central to BPD and MDD are entirely different. The central disturbance of BPD is affective lability, whereas the affective disturbance of MDD is episodic, more sustained, less reactive to the environment, and punctuated by periods of sustained remission. The familiality and phenotypic differences suggest that BPD differs in important ways with respect to symptomatology, prognosis, and heritability; however, very recent twin studies highlight genetic overlap between the two disorders. BPD and MDD comorbidity appears to be most strongly influenced by features of BPD, a revision of Koenigsberg's more bidirectional model, in which each disorder affects the development of the other.

The neurobiological findings in both MDD and BPD are still preliminary at present, and no coherent model for either disorder can be said to have emerged. We have reviewed the overlapping biological processes—amygdala hyperreactivity, volume changes in the subgenual ACC, and deficient serotonergic function—that appear to underlie emotional dysregulation in both disorders. However, the disorders seem to differ in their patterns of brain region involvement, neurohormonal indices, and sleep architecture. At present, the minimal data available for putative genotypes of BPD is still emerging, is nonspecific to the disorder, and demonstrates significant overlap with MDD. The ability to discern commonalities and differences in the neurobiology of these two disorders is limited by the differing methodologies applied in different studies. Definitive clarification of what MDD and BPD have in common and in what ways they are distinct will only be derived from studies that examine both illnesses using the same study design and methodology.

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References

1. Gunderson JG, Elliott GR. The interface between borderline. Am J Psychiatry. 1985;142:277.
2. Gunderson JG, Phillips KA. A current view of the interface between borderline personality disorder and depression. Am J Psychiatry. 1991;148(8):967–75.
3. Koenigsberg HW, Anwunah I, New AS, Mitropoulou V, Schopick F, Siever LJ. Relationship between depression and borderline personality disorder. Depress Anxiety. 1999;10(4): 158–67.
4. Gunderson JG, Morey LC, Stout RL, Skodol AE, Shea MT, McGlashan TH, et al. Major depressive disorder and borderline personality disorder revisited: longitudinal interactions. J Clin Psychiatry. 2004;65(8):1049–56.
5. Plomin R, Owen MJ, McGuffin P. The genetic basis of complex human behaviors. Science. 1994;264(5166):1733–9.
6. Wong AHC, Gottesman II, Petronis A. Phenotypic differences in genetically identical organisms: the epigenetic perspective. Hum Mol Genet. 2005;14 Suppl 1:R11–8.
7. Kendler KS. Genetic epidemiology in psychiatry: taking both genes and environment seriously. Arch Gen Psychiatry. 1995;52(11):895.

8. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Sci Signal. 2003; 301(5631):386.
9. Collins FS, Brooks LD, Chakravarti A. A DNA polymorphism discovery resource for research on human genetic variation. Genome Res. 1998;8(12):1229–31.
10. Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry. 2003;160(4):636–45.
11. Prasad KM, Keshavan MS. Structural cerebral variations as useful endophenotypes in schizophrenia: do they help construct extended endophenotypes? Schizophr Bull. 2008;34(4): 774–90.
12. Balanzá-Martínez V, Rubio C, Selva-Vera G, Martinez-Aran A, Sánchez-Moreno J, Salazar-Fraile J, et al. Neurocognitive endophenotypes (endophenocognitypes) from studies of relatives of bipolar disorder subjects: a systematic review. Neurosci Biobehav Rev. 2008;32(8):1426.
13. Akiskal HS, Chen SE, Davis GC, Puzantian VR, Kahgarian M, Bolinger JM. Borderline: an adjective in search of a noun. J Clin Psychiatry. 1985;46(2):41–8.
14. Sanislow CA, Grilo CM, McGlashan TH. Factor analysis of the DSM-III-R borderline personality disorder criteria in psychiatric inpatients. Am J Psychiatry. 2000;157(10):1629–33.
15. Sanislow CA, Grilo CM, Morey LC, Bender DS, Skodol AE, Gunderson JG, et al. Confirmatory factor analysis of the DSM-IV criteria for borderline personality disorder: findings from the collaborative longitudinal personality disorders study. Am J Psychiatry. 2002; 159(2):284–90.
16. Clifton A, Pilkonis PA. Evidence for a single latent class of Diagnostic and Statistical Manual of Mental Disorders borderline personality pathology. Compr Psychiatry. 2007;48(1):70–8.
17. Fossati A, Madeddu F, Maffei C. Borderline personality disorder and childhood sexual abuse: a meta-analytic study. J Pers Disord. 1999;13(3):268–80.
18. Johansen M, Karterud S, Pedersen G, Gude T, Falkum E. An investigation of the prototype validity of the borderline DSM-IV construct. Acta Psychiatr Scand. 2004;109(4):289–98.
19. Romera I, Delgado-Cohen H, Perez T, Caballero L, Gilaberte I. Factor analysis of the Zung self-rating depression scale in a large sample of patients with major depressive disorder in primary care. BMC Psychiatry. 2008;8(1):4.
20. Pancheri P, Picardi A, Pasquini M, Gaetano P, Biondi M. Psychopathological dimensions of depression: a factor study of the 17-item Hamilton depression rating scale in unipolar depressed outpatients. J Affect Disord. 2002;68(1):41–7.
21. Hasler G, Drevets WC, Manji HK, Charney DS. Discovering endophenotypes for major depression. Neuropsychopharmacology. 2004;29(10):1765–81.
22. Siever LJ, Torgersen S, Gunderson JG, Livesley WJ, Kendler KS. The borderline diagnosis III: identifying endophenotypes for genetic studies. Biol Psychiatry. 2002;51(12):964–8.
23. Gunderson J. Disturbed relationships as a phenotype for borderline personality disorder. Am J Psychiatry. 2007;164(11):1637–40.
24. McGlashan TH, Grilo CM, Skodol AE, Gunderson JG, Shea MT, Morey LC, et al. The Collaborative Longitudinal Personality Disorders Study: baseline Axis I/II and II/II diagnostic co-occurrence. Acta Psychiatr Scand. 2000;102(4):256–64.
25. Skodol AE, Stout RL, McGlashan TH, Grilo CM, Gunderson JG, Shea MT, et al. Co-occurrence of mood and personality disorders: a report from the collaborative longitudinal personality disorders study (CLPS). Depress Anxiety. 1999;10(4):175–82.
26. Silk KR. The quality of depression in borderline personality disorder and the diagnostic process. J Pers Disord. 2010;24(1):25–37.
27. Westen D, Moses MJ, Silk KR, Lohr NE, Cohen R, Segal H. Quality of depressive experience in borderline personality disorder and major depression: when depression is not just depression. J Pers Disord. 1992;6(4):382–93.
28. Rogers JH, Widiger TA, Krupp A. Aspects of depression associated with borderline personality disorder. Am J Psychiatry. 1995;152:268–70.

29. Siever LJ, Klar H, Coccaro E. Psychobiologic substrates of personality. In: Klar H, Siever LJ, editors. Biologic response styles: clinical implications. Washington, DC: American Psychiatric Press; 1985. p. 37–66.
30. Berrocal C, Ruiz Moreno MA, Rando MA, Benvenuti A, Cassano GB. Borderline personality disorder and mood spectrum. Psychiatry Res. 2008;159(3):300–7.
31. Soloff PH, Cornelius J, George A. The depressed borderline: one disorder or two? Psychopharmacol Bull. 1991;27(1):23.
32. Frodl T, Möller HJ, Meisenzahl E. Neuroimaging genetics: new perspectives in research on major depression? Acta Psychiatr Scand. 2008;118(5):363–72.
33. Tranter R, O'Donovan C, Chandarana P, Kennedy S. Prevalence and outcome of partial remission in depression. J Psychiatry Neurosci. 2002;27(4):241.
34. Paris J, Zweig-Frank H. A 27-year follow-up of patients with borderline personality disorder. Compr Psychiatry. 2001;42(6):482–7.
35. Zanarini MC, Frankenburg FR, Reich DB, Hennen J, Silk KR. Adult experiences of abuse reported by borderline patients and Axis II comparison subjects over six years of prospective follow-up. J Nerv Ment Dis. 2005;193(6):412–6.
36. Zanarini M, Frankenburg F, Reich D, Silk K, Hudson J, McSweeney L. The subsyndromal phenomenology of borderline personality disorder: a 10-year follow-up study. Am J Psychiatry. 2007;164(6):929–35.
37. Zanarini MC, Frankenburg FR, Hennen J, Silk KR. Mental health service utilization by borderline personality disorder patients and Axis II comparison subjects followed prospectively for 6 years. J Clin Psychiatry. 2004;65(1):28.
38. Skodol AE, Pagano ME, Bender DS, Shea MT, Gunderson JG, Yen S, et al. Stability of functional impairment in patients with schizotypal, borderline, avoidant, or obsessive-compulsive personality disorder over two years. Psychol Med. 2005;35(3):443–51.
39. Gunderson JG, Stout RL, McGlashan TH, Shea MT, Morey LC, Grilo CM, et al. Ten-year course of borderline personality disorder: psychopathology and function from the Collaborative Longitudinal Personality Disorders Study. Arch Gen Psychiatry. 2011;68(8):827.
40. Sullivan PF, Joyce PR, Mulder RT. Borderline personality disorder in major depression. J Nerv Ment Dis. 1994;182(9):508–16.
41. Gunderson JG, Stout RL, Sanislow CA, Shea MT, McGlashan TH, Zanarini MC, et al. New episodes and new onsets of major depression in borderline and other personality disorders. J Affect Disord. 2008;111(1):40–5.
42. Distel MA, Willemsen G, Ligthart L, Derom CA, Martin NG, Neale MC, et al. Genetic covariance structure of the four main features of borderline personality disorder. J Pers Disord. 2010;24(4):427–44.
43. Kendler KS, Myers J, Reichborn-Kjennerud T. Borderline personality disorder traits and their relationship with dimensions of normative personality: a web-based cohort and twin study. Acta Psychiatr Scand. 2011;123(5):349–59.
44. Distel MA, Middeldorp CM, Trull TJ, Derom CA, Willemsen G, Boomsma DI. Life events and borderline personality features: the influence of gene-environment interaction and gene-environment correlation. Psychol Med. 2011;41(4):849–60.
45. Gunderson JG, Zanarini MC, Choi-Kain LW, Mitchell KS, Jang KL, Hudson JI. Family study of borderline personality disorder and its sectors of psychopathology. Arch Gen Psychiatry. 2011;68(7):753.
46. Kendler KS, Aggen SH, Knudsen GP, Roysamb E, Neale MC, Reichborn-Kjennerud T. The structure of genetic and environmental risk factors for syndromal and subsyndromal common DSM-IV axis I and all axis II disorders. Am J Psychiatry. 2011;168(1):29.
47. White CN, Gunderson JG, Zanarini MC, Hudson JI. Family studies of borderline personality disorder: a review. Harv Rev Psychiatry. 2003;11(1):8–19.
48. Davidson M, Siever J. Affective and impulsive personality disorder traits in the relatives of patients with borderline personality disorder. Am J Psychiatry. 1991;148(1):1378–85.
49. Dahl AA. Heredity in personality disorders—an overview. Clin Genet. 1994;46(1):138–43.

50. Pope Jr HG, Jonas JM, Hudson JI, Cohen BM, Gunderson JG. The validity of DSM-III borderline personality disorder: a phenomenologic, family history, treatment response, and long-term follow-up study. Arch Gen Psychiatry. 1983;40(1):23.
51. Zanarini MC, Gunderson JG, Marino MF, Schwartz EO, Frankenburg FR. DSM-III disorders in the families of borderline outpatients. J Pers Disord. 1988;2(4):292–302.
52. Riso LP, Klein DN, Anderson RL, Ouimette PC. A family study of outpatients with borderline personality disorder and no history of mood disorder. J Pers Disord. 2000;14(3): 208–17.
53. Kendler KS, Aggen SH, Czajkowski N, Roysamb E, Tambs K, Torgersen S, et al. The structure of genetic and environmental risk factors for DSM-IV personality disorders: a multivariate twin study. Arch Gen Psychiatry. 2008;65(12):1438.
54. Torgersen S. Genetics of patients with borderline personality disorder. Psychiatr Clin North Am. 2000;23(1):1–9.
55. Belsky DW, Caspi A, Arseneault L, Bleidorn W, Fonagy P, Goodman M, et al. Etiological features of borderline personality related characteristics in a birth cohort of 12-year-old children. Dev Psychopathol. 2012;24(1):251.
56. Reichborn-Kjennerud T, Czajkowski N, Røysamb E, Ørstavik RE, Neale MC, Torgersen S, et al. Major depression and dimensional representations of DSM-IV personality disorders: a population-based twin study. Psychol Med. 2010;40(9):1475–84.
57. Kendler KS, Prescott CA. A population-based twin study of lifetime major depression in men and women. Arch Gen Psychiatry. 1999;56(1):39.
58. Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: review and meta-analysis. Am J Psychiatry. 2000;157(10):1552–62.
59. Kendler KS, Gardner CO, Prescott CA. Clinical characteristics of major depression that predict risk of depression in relatives. Arch Gen Psychiatry. 1999;56(4):322.
60. Ni X, Bismil R, Chan K, Sicard T, Bulgin N, McMain S, et al. Serotonin 2A receptor gene is associated with personality traits, but not to disorder, in patients with borderline personality disorder. Neurosci Lett. 2006;408(3):214–9.
61. Cadoret RJ, Langbehn D, Caspers K, Troughton EP, Yucuis R, Sandhu HK, et al. Associations of the serotonin transporter promoter polymorphism with aggressivity, attention deficit, and conduct disorder in an adoptee population. Compr Psychiatry. 2003;44(2):88–101.
62. Sen S, Villafuerte S, Nesse R, Stoltenberg SF, Hopcian J, Gleiberman L, et al. Serotonin transporter and GABA (A) alpha 6 receptor variants are associated with neuroticism. Biol Psychiatry. 2004;55:244–9.
63. Maurex L, Zaboli G, Öhman A, Asberg M, Leopardi R. The serotonin transporter gene polymorphism (5-HTTLPR) and affective symptoms among women diagnosed with borderline personality disorder. Eur Psychiatry. 2010;25(1):19–25.
64. Pascual JC, Soler J, Barrachina J, Campins MJ, Alvarez E, Perez V, et al. Failure to detect an association between the serotonin transporter gene and borderline personality disorder. J Psychiatr Res. 2008;42(1):87–8.
65. Zaboli G, Gizatullin R, Nilsonne A, Wilczek A, Jonsson EG, Ahnemark E, et al. Tryptophan hydroxylase-1 gene variants associate with a group of suicidal borderline women. Neuropsychopharmacology. 2006;31(9):1982–90.
66. Wilson ST, Stanley B, Brent DA, Oquendo MA, Huang YY, Haghighi F, et al. Interaction between Tryptophan Hydroxylase I (TPH1) polymorphisms and childhood abuse is associated with increased risk for borderline personality disorder in adulthood. Psychiatr Genet. 2012;22(1):15.
67. Maurex L, Zaboli G, Wiens S, Ãsberg M, Leopardi R, Ohman A. Emotionally controlled decision-making and a gene variant related to serotonin synthesis in women with borderline personality disorder. Scand J Psychol. 2009;50(1):5–10.
68. Wilson ST, Stanley B, Brent DA, Oquendo MA, Huang YY, Mann JJ. The tryptophan hydroxylase-1 A218C polymorphism is associated with diagnosis, but not suicidal behavior, in borderline personality disorder. Am J Med Genet B Neuropsychiatr Genet. 2009; 150(2):202–8.

69. Ni X, Chan D, Chan K, McMain S, Kennedy JL. Serotonin genes and gene-gene interactions in borderline personality disorder in a matched case-control study. Prog Neuropsychopharmacol Biol Psychiatry. 2009;33(1):128–33.
70. Perez-Rodriguez M, Weinstein S, New AS, Bevilacqua L, Yuan Q, Zhou Z, et al. Tryptophan-hydroxylase 2 haplotype association with borderline personality disorder and aggression in a sample of patients with personality disorders and healthy controls. J Psychiatr Res. 2010; 44(15):1075–81.
71. Ni X, Sicard T, Bulgin N, Bismil R, Chan K, McMain S, et al. Monoamine oxidase A gene is associated with borderline personality disorder. Psychiatr Genet. 2007;17(3):153–7.
72. Ni X, Chan K, Bulgin N, Sicard T, Bismil R, McMain S, et al. Association between serotonin transporter gene and borderline personality disorder. J Psychiatr Res. 2006;40(5):448–53.
73. Tadić A, Elsäßerr A, Victor A, von Cube R, Başkaya Ö, Wagner S, et al. Association analysis of serotonin receptor 1B (HTR1B) and brain-derived neurotrophic factor gene polymorphisms in Borderline personality disorder. J Neural Transm. 2009;116(9):1185–8.
74. Joyce PR, McHugh PC, Light KJ, Rowe S, Miller AL, Kennedy MA. Relationships between angry-impulsive personality traits and genetic polymorphisms of the dopamine transporter. Biol Psychiatry. 2009;66(8):717–21.
75. Wagner S, Başkaya Ö, Anicker NJ, Dahmen N, Lieb K, Tadić A. The catechol-o-methyltransferase (COMT) val158met polymorphism modulates the association of serious life events (SLE) and impulsive aggression in female patients with borderline personality disorder (BPD). Acta Psychiatr Scand. 2010;122(2):110–7.
76. Dammann G, Teschler S, Haag T, Altmüller F, Tuczek F, Dammann RH. Increased DNA methylation of neuropsychiatric genes occurs in borderline personality disorder. Epigenetics. 2011;6(12):1454–62.
77. Anguelova M, Benkelfat C, Turecki G. A systematic review of association studies investigating genes coding for serotonin receptors and the serotonin transporter: II. Suicidal behavior. Mol Psychiatry. 2003;8(7):646–53.
78. Bellivier F, Laplanche J-L, Leboyer M, Feingold J. Serotonin transporter gene and manic depressive illness: an association study. Biol Psychiatry. 1997;41(6):750–2.
79. Liu W, Gu N, Feng G, Li S, Bai S, Zhang J, et al. Tentative association of the serotonin transporter with schizophrenia and unipolar depression but not with bipolar disorder in Han Chinese. Pharmacogenet Genomics. 1999;9(4):491–5.
80. Furlong RA, Ho L, Walsh C, Rubinsztein JS, Jain S, Paykel ES, et al. Analysis and meta-analysis of two serotonin transporter gene polymorphisms in bipolar and unipolar affective disorders. Am J Med Genet. 1998;81(1):58–63.
81. Hoehe MR, Wendel B, Grunewald I, Chiaroni P, Levy N, Morris-Rosendahl D, et al. Brief research communication: serotonin transporter (5-HTT) gene polymorphisms are not associated with susceptibility to mood disorders. Am J Med Genet. 1998;81(1):1–3.
82. Minov C, Baghai TC, Schule C, Zwanzger P, Schwarz MJ, Zill P, et al. Serotonin-2A-receptor and-transporter polymorphisms: lack of association in patients with major depression. Neurosci Lett. 2001;303(2):119–22.
83. Oliveira JR, Carvalho DR, Pontual D, Gallindo RM, Sougey EB, Gentil V, et al. Analysis of the serotonin transporter polymorphism (5-HTTLPR) in Brazilian patients affected by dysthymia, major depression and bipolar disorder. Mol Psychiatry. 2000;5(4):348.
84. Aleman A, Swart M, van Rijn S. Brain imaging, genetics and emotion. Biol Psychol. 2008;79(1):58–69.
85. Pezawas L, Meyer-Lindenberg A, Drabant EM, Verchinski BA, Munoz KE, Kolachana BS, et al. 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. Nat Neurosci. 2005;8(6):828–34.
86. McMahon FJ, Buervenich S, Charney D, Lipsky R, Rush AJ, Wilson AF, et al. Variation in the gene encoding the serotonin 2A receptor is associated with outcome of antidepressant treatment. Am J Hum Genet. 2006;78(5):804.
87. Zill P, Baghai TC, Zwanzger P, Schule C, Eser D, Rupprecht R, et al. SNP and haplotype analysis of a novel tryptophan hydroxylase isoform (TPH2) gene provide evidence for association with major depression. Mol Psychiatry. 2004;9(11):1030–6.

88. Drevets WC, Thase M, Moses E, Price J, Frank E, Kupfer DJ, et al. Serotonin-1A receptor imaging in recurrent depression: replication and literature review. Nucl Med Biol. 2007; 34(7):865.
89. Ke L, Qi ZY, Ping Y, Ren CY. Effect of SNP at position 40237 in exon 7 of the TPH2 gene on susceptibility to suicide. Brain Res. 2006;1122(1):24–6.
90. Zhou Z, Roy A, Lipsky R, Kuchipudi K, Zhu G, Taubman J, et al. Haplotype-based linkage of tryptophan hydroxylase 2 to suicide attempt, major depression, and cerebrospinal fluid 5-hydroxyindoleacetic acid in 4 populations. Arch Gen Psychiatry. 2005;62(10):1109.
91. Mickey BJ, Ducci F, Hodgkinson CA, Langenecker SA, Goldman D, Zubieta J-K. Monoamine oxidase A genotype predicts human serotonin 1A receptor availability in vivo. J Neurosci. 2008;28(44):11354–9.
92. Schulze TG, Muller DJ, Krauss H, Scherk H, Ohlraun S, Syagailo YV, et al. Association between a functional polymorphism in the monoamine oxidase A gene promoter and major depressive disorder. Am J Med Genet. 2000;96(6):801–3.
93. Domschke K, Hohoff C, Mortensen LS, Roehrs T, Deckert J, Arolt V, et al. Monoamine oxidase a variant influences antidepressant treatment response in female patients with major depression. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32(1):224–8.
94. Duman RS, Monteggia LM. A neurotrophic model for stress-related mood disorders. Biol Psychiatry. 2006;59(12):1116.
95. Lohoff FW, Sander T, Ferraro TN, Dahl JP, Gallinat J, Berrettini WH. Confirmation of association between the Val66Met polymorphism in the brain-derived neurotrophic factor (BDNF) gene and bipolar I disorder. Am J Med Genet B Neuropsychiatr Genet. 2005; 139(1):51–3.
96. Schumacher J, Jamra RA, Becker T, Ohlraun S, Klopp N, Binder EB, et al. Evidence for a relationship between genetic variants at the brain-derived neurotrophic factor (BDNF) locus and major depression. Biol Psychiatry. 2005;58(4):307–14.
97. Surtees PG, Wainwright NWJ, Willis-Owen SAG, Sandhu MS, Luben R, Day NE, et al. No association between the BDNF Val66Met polymorphism and mood status in a non-clinical community sample of 7389 older adults. J Psychiatr Res. 2007;41(5):404–9.
98. New AS, Trestman RL, Mitropoulou V, Benishay DS, Coccaro E, Silverman J, et al. Serotonergic function and self-injurious behavior in personality disorder patients. Psychiatry Res. 1997;69(1):17.
99. Kavoussi R, Armstead P, Coccaro E. The neurobiology of impulsive aggression. Psychiatr Clin North Am. 1997;20(2):395–403.
100. Heuser I, Yassouridis A, Holsboer F. The combined dexamethasone/CRH test: a refined laboratory test for psychiatric disorders. J Psychiatr Res. 1994;28(4):341–56.
101. Holsboer F, Lauer CJ, Schreiber W, Krieg J-C. Altered hypothalamic-pituitary-adrenocortical regulation in healthy subjects at high familial risk for affective disorders. Neuroendocrinology. 2008;62(4):340–7.
102. Southwick SM, Vythilingam M, Charney DS. The psychobiology of depression and resilience to stress: implications for prevention and treatment*. Annu Rev Clin Psychol. 2005;1: 255–91.
103. Grossman R, Yehuda R, New A, Schmeidler J, Silverman J, Mitropoulou V, et al. Dexamethasone suppression test findings in subjects with personality disorders: associations with posttraumatic stress disorder and major depression. Am J Psychiatry. 2003;160(7): 1291–8.
104. Lange W, Wulff H, Berea C, Beblo T, Saavedra AS, Mensebach C, et al. Dexamethasone suppression test in borderline personality disorder–effects of posttraumatic stress disorder. Psychoneuroendocrinology. 2005;30(9):919.
105. Rinne T, De Kloet ER, Wouters L, Goekoop JG, DeRijk RH, van den Brink W. Hyperresponsiveness of hypothalamic-pituitary-adrenal axis to combined dexamethasone/corticotropin-releasing hormone challenge in female borderline personality disorder subjects with a history of sustained childhood abuse. Biol Psychiatry. 2002;52(11):1102.

106. Wingenfeld K, Spitzer C, Rullkötter N, Löwe B. Borderline personality disorder: hypothalamus pituitary adrenal axis and findings from neuroimaging studies. Psychoneuroendocrinology. 2010;35(1):154–70.
107. Carrasco JL, Díaz-Marsá M, Pastrana JI, Molina R, Brotons L, López-Ibor MI, et al. Hypothalamic–pituitary–adrenal axis response in borderline personality disorder without post-traumatic features. Br J Psychiatry. 2007;190(4):357–8.
108. Walter M, Bureau J-F, Holmes BM, Bertha EA, Hollander M, Wheelis J, et al. Cortisol response to interpersonal stress in young adults with borderline personality disorder: a pilot study. Eur Psychiatry. 2008;23(3):201–4.
109. De la Fuente JM, Bobes J, Vizuete C, Mendlewicz J. Biological nature of depressive symptoms in borderline personality disorder: endocrine comparison to recurrent brief and major depression. J Psychiatr Res. 2002;36(3):137–45.
110. Giles DE, Jarrett RB, Rush AJ, Biggs MM, Roffwarg HP. Prospective assessment of electroencephalographic sleep in remitted major depression. Psychiatry Res. 1993;46(3):269–84.
111. Modell S, Huber J, Holsboer F, Lauer CJ. The Munich vulnerability study on affective disorders: risk factors for unipolarity versus bipolarity. J Affect Disord. 2003;74(2):173–84.
112. Murck H, Nickel T, Kunzel H, Antonijevic IA, Schill J, Zobel A, et al. State markers of depression in sleep EEG: dependency on drug and gender in patients treated with tianeptine or paroxetine. Neuropsychopharmacology. 2003;28(2):348–58.
113. Graves LA, Hellman K, Veasey S, Blendy JA, Pack AI, Abel T. Genetic evidence for a role of CREB in sustained cortical arousal. J Neurophysiol. 2003;90(2):1152–9.
114. Bastien CH, Guimond S, St-Jean G, Lemelin S. Signs of insomnia in borderline personality disorder individuals. J Clin Sleep Med. 2008;4(5):462.
115. Simor PT, Horváth KR. Altered sleep in Borderline Personality Disorder in relation to the core dimensions of psychopathology. Scand J Psychol. 2013;54(4):300–12.
116. Fleischer M, Schäfer M, Coogan A, Häßler F, Thome J. Sleep disturbances and circadian CLOCK genes in borderline personality disorder. J Neural Transm. 2012;119(10):1105–10.
117. Battaglia M, Ferini-Strambi L, Smirne S, Bernardeschi L, Bellodi L. Ambulatory polysomnography of never-depressed borderline subjects: a high-risk approach to rapid eye movement latency. Biol Psychiatry. 1993;33(5):326–34.
118. Lahmeyer HW, Reynolds 3rd CF, Kupfer DJ, King R. Biologic markers in borderline personality disorder: a review. J Clin Psychiatry. 1989;50(6):217.
119. De la Fuente JM, Bobes J, Vizuete C, Mendlewicz J. Sleep-EEG in borderline patients without concomitant major depression: a comparison with major depressives and normal control subjects. Psychiatry Res. 2001;105(1–2):87–95.
120. Kupfer DJ, Frank E, Phillips ML. Major depressive disorder: new clinical, neurobiological, and treatment perspectives. Lancet. 2012;379(9820):1045–55.
121. Frodl T, Meisenzahl EM, Zetzsche T, Höhne T, Banac S, Schorr C, et al. Hippocampal and amygdala changes in patients with major depressive disorder and healthy controls during a 1-year follow-up. J Clin Psychiatry. 2004;65(4):492–9.
122. Mervaala E, Fohr J, Kononen M, Valkonen-Korhonen M, Vainio P, Partanen K, et al. Quantitative MRI of the hippocampus and amygdala in severe depression. Psychol Med. 2000;30(1):117–25.
123. Hamilton JP, Siemer M, Gotlib IH. Amygdala volume in major depressive disorder: a meta-analysis of magnetic resonance imaging studies. Mol Psychiatry. 2008;13(11):993–1000.
124. Driessen M, Herrmann J, Stahl K, Zwaan M, Meier S, Hill A, et al. Magnetic resonance imaging volumes of the hippocampus and the amygdala in women with borderline personality disorder and early traumatization. Arch Gen Psychiatry. 2000;57(12):1115.
125. Hall J, Olabi B, Lawrie SM, McIntosh AM. Hippocampal and amygdala volumes in borderline personality disorder: a meta-analysis of magnetic resonance imaging studies. Pers Mental Health. 2010;4(3):172–9.
126. Nunes PM, Wenzel A, Borges KT, Porto CR, Caminha RM, de Oliveira IR. Volumes of the hippocampus and amygdala in patients with borderline personality disorder: a meta-analysis. J Pers Disord. 2009;23(4):333–45.

127. O'Neill A, Frodl T. Brain structure and function in borderline personality disorder. Brain Struct Funct. 2012;217(4):767–82.
128. Ruocco AC, Amirthavasagam S, Zakzanis KK. Amygdala and hippocampal volume reductions as candidate endophenotypes for borderline personality disorder: a meta-analysis of magnetic resonance imaging studies. Psychiatry Res. 2012;201(3):245–52.
129. Brambilla P, Soloff PH, Sala M, Nicoletti MA, Keshavan MS, Soares JC. Anatomical MRI study of borderline personality disorder patients. Psychiatry Res. 2004;131(2):125–33.
130. New AS, Hazlett EA, Buchsbaum MS, Goodman M, Mitelman SA, Newmark R, et al. Amygdala-prefrontal disconnection in borderline personality disorder. Neuropsychopharmacology. 2007;32(7):1629–40.
131. Zetzsche T, Frodl T, Preuss UW, Schmitt G, Seifert D, Leinsinger G, et al. Amygdala volume and depressive symptoms in patients with borderline personality disorder. Biol Psychiatry. 2006;60(3):302–10.
132. Siegle GJ, Konecky RO, Thase ME, Carter CS. Relationships between amygdala volume and activity during emotional information processing tasks in depressed and never-depressed individuals. Ann N Y Acad Sci. 2003;985(1):481–4.
133. Drevets WC, Bogers W, Raichle ME. Functional anatomical correlates of antidepressant drug treatment assessed using PET measures of regional glucose metabolism. Eur Neuropsychopharmacol. 2002;12(6):527–44.
134. Sheline YI, Barch DM, Donnelly JM, Ollinger JM, Snyder AZ, Mintun MA. Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. Biol Psychiatry. 2001;50(9):651–8.
135. Canli T, Cooney RE, Goldin P, Shah M, Sivers H, Thomason ME, et al. Amygdala reactivity to emotional faces predicts improvement in major depression. Neuroreport. 2005;16(12):1267–70.
136. Schmahl C, Bohus M, Esposito F, Treede R-D, Di Salle F, Greffrath W, et al. Neural correlates of antinociception in borderline personality disorder. Arch Gen Psychiatry. 2006;63(6):659.
137. Donegan NH, Sanislow CA, Blumberg HP, Fulbright RK, Lacadie C, Skudlarski P, et al. Amygdala hyperreactivity in borderline personality disorder: implications for emotional dysregulation. Biol Psychiatry. 2003;54(11):1284–93.
138. Schulze L, Domes G, Krüger A, Berger C, Fleischer M, Prehn K, et al. Neuronal correlates of cognitive reappraisal in borderline patients with affective instability. Biol Psychiatry. 2011;69(6):564–73.
139. Hazlett EA, Zhang J, New AS, Zelmanova Y, Goldstein KE, Haznedar MM, et al. Potentiated amygdala response to repeated emotional pictures in borderline personality disorder. Biol Psychiatry. 2012;72(6):448–56.
140. Kraus A, Valerius G, Seifritz E, Ruf M, Bremner JD, Bohus M, et al. Script-driven imagery of self-injurious behavior in patients with borderline personality disorder: a pilot FMRI study. Acta Psychiatr Scand. 2010;121(1):41–51.
141. Coccaro EF, McCloskey MS, Fitzgerald DA, Phan KL. Amygdala and orbitofrontal reactivity to social threat in individuals with impulsive aggression. Biol Psychiatry. 2007;62(2):168–78.
142. Kamphausen S, SchrÖder P, Maier S, Bader K, Feige B, Kaller CP, et al. Medial prefrontal dysfunction and prolonged amygdala response during instructed fear processing in borderline personality disorder. World J Biol Psychiatry. 2013;14(4):307–18.
143. Minzenberg MJ, Fan J, New AS, Tang CY, Siever LJ. Frontolimbic dysfunction in response to facial emotion in borderline personality disorder: an event-related fMRI study. Psychiatry Res. 2007;155(3):231.
144. Ruocco AC, Amirthavasagam S, Choi-Kain LW, McMain SF. Neural correlates of negative emotionality in borderline personality disorder: an activation-likelihood-estimation meta-analysis. Biol Psychiatry. 2013;73(2):153–60.

145. Coryell W, Nopoulos P, Drevets W, Wilson T, Andreasen NC. Subgenual prefrontal cortex volumes in major depressive disorder and schizophrenia: diagnostic specificity and prognostic implications. Am J Psychiatry. 2005;162(9):1706–12.
146. Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, et al. Deep brain stimulation for treatment-resistant depression. Neuron. 2005;45(5):651–60.
147. Diener C, Kuehner C, Brusniak W, Ubl B, Wessa M, Flor H. A meta-analysis of neurofunctional imaging studies of emotion and cognition in major depression. Neuroimage. 2012; 61(3):677–85.
148. Siegle G. Brain mechanisms of borderline personality disorder at the intersection of cognition, emotion, and the clinic. Am J Psychiatry. 2007;164(12):1776–9.
149. Drevets WC, Price JL, Furey ML. Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. Brain Struct Funct. 2008; 213(1–2):93–118.
150. Hazlett EA, Speiser LJ, Goodman M, Roy M, Carrizal M, Wynn JK, et al. Exaggerated affect-modulated startle during unpleasant stimuli in borderline personality disorder. Biol Psychiatry. 2007;62(3):250–5.
151. Minzenberg MJ, Fan J, New AS, Tang CY, Siever LJ. Frontolimbic structural changes in borderline personality disorder. J Psychiatr Res. 2008;42(9):727.
152. Hazlett EA, New AS, Newmark R, Haznedar MM, Lo JN, Speiser LJ, et al. Reduced anterior and posterior cingulate gray matter in borderline personality disorder. Biol Psychiatry. 2005; 58(8):614–23.
153. Schnell K, Dietrich T, Schnitker R, Daumann J, Herpertz SC. Processing of autobiographical memory retrieval cues in borderline personality disorder. J Affect Disord. 2007;97(1–3): 253–9.
154. Silbersweig D, Clarkin J, Goldstein M, Kernberg O, Tuescher O, Levy K, et al. Failure of frontolimbic inhibitory function in the context of negative emotion in borderline personality disorder. Am J Psychiatry. 2007;164(12):1832–41.
155. Siever LJ, Buchsbaum MS, New AS, Spiegel-Cohen J, Wei T, Hazlett EA, et al. d, l-fenfluramine response in impulsive personality disorder assessed with [18 F] fluorodeoxyglucose positron emission tomography. Neuropsychopharmacology. 1999;20(5):413–23.
156. New A, Hazlett E, Buchsbaum MS, Goodman M, Reynolds D, Mitropoulou V, et al. Blunted prefrontal cortical 18fluorodeoxyglucose positron emission tomography response to meta-chloropiperazine in impulsive aggression. Arch Gen Psychiatry. 2002;59(7):621–9.
157. Soloff PH, Meltzer CC, Becker C, Greer PJ, Kelly TM, Constantine D. Impulsivity and prefrontal hypometabolism in borderline personality disorder. Psychiatry Res. 2003;123(3):153.
158. da Rocha FF, Malloy-Diniz L, De Sousa K, Prais H, Correa H, Teixeira AL. Borderline personality features possibly related to cingulate and orbitofrontal cortices dysfunction due to schizencephaly. Clin Neurol Neurosurg. 2008;110(4):396.
159. Bremner JD, Narayan M, Anderson ER, Staib LH, Miller HL, Charney DS. Hippocampal volume reduction in major depression. Am J Psychiatry. 2000;157(1):115–8.
160. Von Gunten A, Fox NC, Cipolotti L, Ron MA. A volumetric study of hippocampus and amygdala in depressed patients with subjective memory problems. J Neuropsychiatry Clin Neurosci. 2000;12(4):493–8.
161. Videbech P, Ravnkilde B. Hippocampal volume and depression: a meta-analysis of MRI studies. Am J Psychiatry. 2004;161(11):1957–66.
162. Kempton MJ, Salvador Z, Munafo MR, Geddes JR, Simmons A, Frangou S, et al. Structural neuroimaging studies in major depressive disorder: meta-analysis and comparison with bipolar disorder. Arch Gen Psychiatry. 2011;68(7):675.
163. Sheline YI, Wang PW, Gado MH, Csernansky JG, Vannier MW. Hippocampal atrophy in recurrent major depression. Proc Natl Acad Sci. 1996;93(9):3908–13.
164. Chanen AM, Velakoulis D, Carison K, Gaunson K, Wood SJ, Yuen HP, et al. Orbitofrontal, amygdala and hippocampal volumes in teenagers with first-presentation borderline personality disorder. Psychiatry Res. 2008;163(2):116–25.

165. Schmahl CG, Vermetten E, Elzinga BM, Douglas Bremner J. Magnetic resonance imaging of hippocampal and amygdala volume in women with childhood abuse and borderline personality disorder. Psychiatry Res. 2003;122(3):193–8.
166. Zetzsche T, Preuss UW, Frodl T, Schmitt G, Seifert D, Münchhausen E, et al. Hippocampal volume reduction and history of aggressive behaviour in patients with borderline personality disorder. Psychiatry Res. 2007;154(2):157–70.
167. Irle E, Lange C, Sachsse U. Reduced size and abnormal asymmetry of parietal cortex in women with borderline personality disorder. Biol Psychiatry. 2005;57(2):173–82.
168. Rodrigues E, Wenzel A, Ribeiro MP, Quarantini LC, Miranda-Scippa A, de Sena EP, et al. Hippocampal volume in borderline personality disorder with and without comorbid posttraumatic stress disorder: a meta-analysis. Eur Psychiatry. 2011;26(7):452–6.
169. Lange C, Kracht L, Herholz K, Sachsse U, Irle E. Reduced glucose metabolism in temporoparietal cortices of women with borderline personality disorder. Psychiatry Res. 2005; 139(2):115–26.
170. Stockmeier CA. Involvement of serotonin in depression: evidence from postmortem and imaging studies of serotonin receptors and the serotonin transporter. J Psychiatr Res. 2003; 37(5):357–73.
171. Leyton M, Okazawa H, Diksic M, Paris J, Rosa P, Mzengeza S, et al. Brain regional a-[11C] Methyl-L-Tryptophan trapping in impulsive subjects with borderline personality disorder. Am J Psychiatry. 2001;158(5):775–82.
172. Soloff PH, Price JC, Meltzer CC, Fabio A, Frank GK, Kaye WH. 5HT2A receptor binding is increased in borderline personality disorder. Biol Psychiatry. 2007;62(6):580–7.
173. Frankle WG, Lombardo I, New AS, Goodman M, Talbot PS, Huang Y, et al. Brain serotonin transporter distribution in subjects with impulsive aggressivity: a positron emission study with [11C] McN 5652. Am J Psychiatry. 2005;162(5):915–23.

Chapter 3
Borderline Personality Disorder, Atypical Depression, and Cyclothymia: Diagnostic Distinctions Crossing Mood and Personality Disorders Borders

Lois W. Choi-Kain and Ana M. Rodriguez-Villa

Introduction

Patients who present with symptoms of affective instability, behavioral impulsivity, and interpersonal rejection sensitivity will be variably diagnosed with atypical depression, bipolar disorder, or borderline personality disorder (BPD), depending on the clinician who sees them. In both primary care and mental health services, the assessment of mood symptoms (i.e., SIGECAPS and DIGFAST) serves as a gateway into evaluating any psychiatric disorder. Consequently, many individuals who have some variation of mood problems will sort primarily into a mood disorder diagnosis, even if they have a more definitive diagnosis, like BPD, which can either explain or co-occur with mood symptoms. A common assumption driving this trend is that psychopharmacologic management is relatively easy to learn and concrete in its administration, while learning manualized psychotherapies for BPD is too time intensive, expensive, and specialized for the generalist mental health practitioner.

As reviewed in this volume by numerous authors (Paris, Goodman, Morgan & Zimmerman, Reich, Silk), the mood problems of individuals with BPD are distinct and divergent from diagnostic criteria for both major depressive disorder and bipolar disorder. The spectrum of variants on usual presentations for mood disorders—which include atypical depression, bipolar II, ultrarapid cycling bipolar, and cyclothymia—has expanded to capture the constellation of symptoms presented by patients who are classically borderline. The tendency to confuse or collapse the BPD diagnosis into a mood disorder spectrum bears significantly on clinical practice as it suggests an algorithm of treatments that are not only limited

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in their evidentiary bases and efficacy in a personality-disordered subset of patients but also diverts clinical interventions away from more effective forms of treatments [1]. In these instances, patients may undergo lengthy medication trials, which become more complex and toxic, since simple, benign regimens are likely to fail as a primary or central therapeutic solution. By the time a patient preliminarily diagnosed with a mood disorder is properly diagnosed with BPD, they may have acquired many more iatrogenic problems including dependence on prescribed medications (e.g., benzodiazepines [2] and stimulants), weight gain, and sedation [3, 4]. When untreated BPD-related dysfunction combines with a layer of iatrogenic medication-induced problems, patients are prone to miss formative developmental experiences in their adolescent and young adult years (e.g., leaving home for college, starting a career, building peer networks) which tend to stabilize, structure, and organize interpersonal functioning and identity formation. These problems—avoidable if proper diagnosis is not delayed by a preliminary mood disorders approach—may compound problems of BPD with other sources of serious dysfunction.

The irony of this problem is this: while many clinicians practice with the assumption that mood disorders are more straightforward to treat, the evidence base for the treatment of atypical depression, bipolar depression, and cyclothymia are inconclusive at best [5–7]. In contrast, the evidentiary base which validates the efficacy of manualized psychotherapies designed specifically for BPD is robust and provides many pathways for significant reduction in symptoms, including in the depressive and anxious realms [8, 9]. These evidence-based treatments for BPD do not carry the risk burden of psychopharmacologic agents (i.e., toxic side effects and lethality in overdose) and address the underlying temperamental liabilities more directly.

In efforts to clarify the optimal clinical pathway among patients with a differential diagnosis of atypical depression, cyclothymia, and borderline personality disorders, this chapter will review the diagnostic criteria and confusions between these disorders, historical bases for their conceptualization, empirical overlaps, and specific evidence-based treatment approaches. In reviewing the confusions and controversies related to the diagnosis and treatment of atypical depression, bipolar spectrum, and borderline personality disorders, readers will be able to clarify the costs and benefits for pursuing different diagnostic distinctions and their relevant treatment algorithms.

Definitions: Overlaps and Distinctions

The controversy around the diagnostic overlaps between mood disorders and BPD has raged on since the 1980s. Among the most prominent critic of the BPD diagnosis, Hagop Akiskal [10] has argued that BPD is a toxic misnomer for patients who have mood disorders. Throughout this book, multiple authors have described the epidemiologic, biological, and phenomenological overlaps and distinctions between major depressive disorder, bipolar disorder types I and II, and BPD. For this reason,

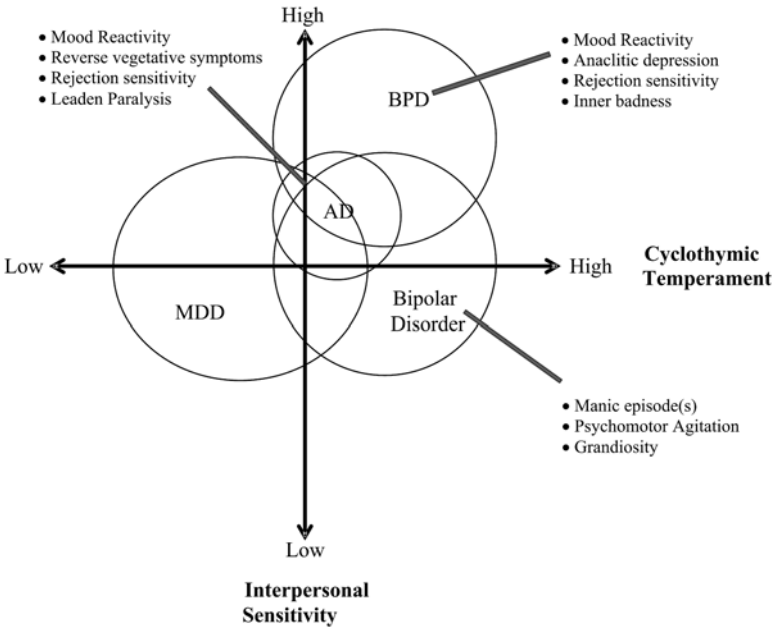

Fig. 3.1 Cyclothymia and interpersonal sensitivity in major depression, atypical depression, bipolar disorder, and borderline personality disorder

this chapter will not discuss as its main focus major depressive disorder or bipolar type I and II disorders. This chapter explores more specifically the relationship between BPD and the *atypical* mood disorder variants—atypical depression and cyclothymia—used to describe the unique affective presentations of individuals with a constellation of mood, personality, and temperamental features that defy traditional diagnostic classification and respond suboptimally or atypically to pharmacologic interventions.

The diagnostic criteria for these disorders overlap significantly (Fig. 3.1). Atypical depression extends the boundaries of usual mood disorder features in its inclusion of interpersonal rejection sensitivity as part of its diagnostic criteria. Cyclothymia is a term used in two ways: (1) it describes a mood disorder with hypomanic and depressive mood features that alternate but do not reach full threshold of major depressive, manic, or hypomanic criteria [11] and (2) it describes a temperamental trait or underlying personality organized around an "inherent disposition of affective dysregulation" [12]. Both atypical depression and cyclothymia capture the more dysphoric and affectively unstable aspects of borderline psychopathology. Preliminary research investigating the relationship between these disorders suggests that cyclothymic temperament is a fundamental underlying diathesis of both atypical depression and BPD [13], suggesting a theory for the overlap between all three disorders. However, the overlaps between

these diagnostic entities are incomplete, suggesting that they converge in specific characteristics but are also distinct and not interchangeable.

Starting with a historical review of the development of these diagnostic entities, this section will review the overlaps and distinctions among atypical depression, cyclothymia, and BPD to clarify the way these diagnostic concepts capture various dimensions of similar complex clinical presentations that span multiple diagnostic categories. The historical development of these diagnoses, particularly atypical depression and BPD, overlaps considerably, representing two parallel streams of effort aimed to better understand a group of patients who neither conformed to typical diagnostic definitions nor responded to typical treatments. The limited empirical literature on the individual features of these illnesses and how they overlap will also be reviewed. Lastly, treatment approaches and future directions for research will be considered to guide readers towards a more integrated and empirically informed approach to these complex and atypical patient presentations.

Historical Overlaps (Fig. 3.2)

Atypical Depression

The term atypical depression was coined in the 1950s to describe a group of patients particularly responsive to monoamine oxidase inhibitors (MAOIs), in contrast to more typical patients with endogenous or melancholic depression, who responded to electroconvulsive therapy (ECT) and tricyclic antidepressants (TCAs) [14, 15]. Once psychiatric researchers identified this divergence in treatment response, they began to retrospectively characterize clinical features which separated these patients. Central to the descriptions of the patients with this variant of atypical depression was the prominence of anxiety, with associated features of severe fatigue, weight gain, evening worsening, somatic preoccupation, and premenstrual tension [14, 15]. Depression was of "secondary importance" and characterized as "reactive" and "exogenous" [16]. Both the depression and the personalities of these atypical patients were described as hysterical [15, 17]. In its earliest descriptions, atypical depression seemed to characterize patients who did not respond to typical antidepressant treatments because of the prominence of anxiety and personality features.

Further elaboration of the personality styles associated with atypical depression occurred in the 1960s to 1980s. The term "hysteroid dysphoria" was used to signify a type of depressive dysphoria and mood reactivity seen in "histrionic" women with MAOI-responsive symptoms [18–20]. The cardinal feature of hysteroid dysphoria was the sensitivity of mood and exaggerated behavioral reactivity to romantic relationships. At the loss of romantic relationships, these patients would demonstrate anger, hostility, dysphoria, and at times suicidality. In this rejected and dysphoric state, these patients exhibited a tendency to oversleep and overeat, particularly craving chocolate and sweets. Conversely, in responses to positive romantic developments, these patients would present as euphoric or giddy [18]. The clinical phenomenology of hysteroid dysphoria overlaps significantly with that of both

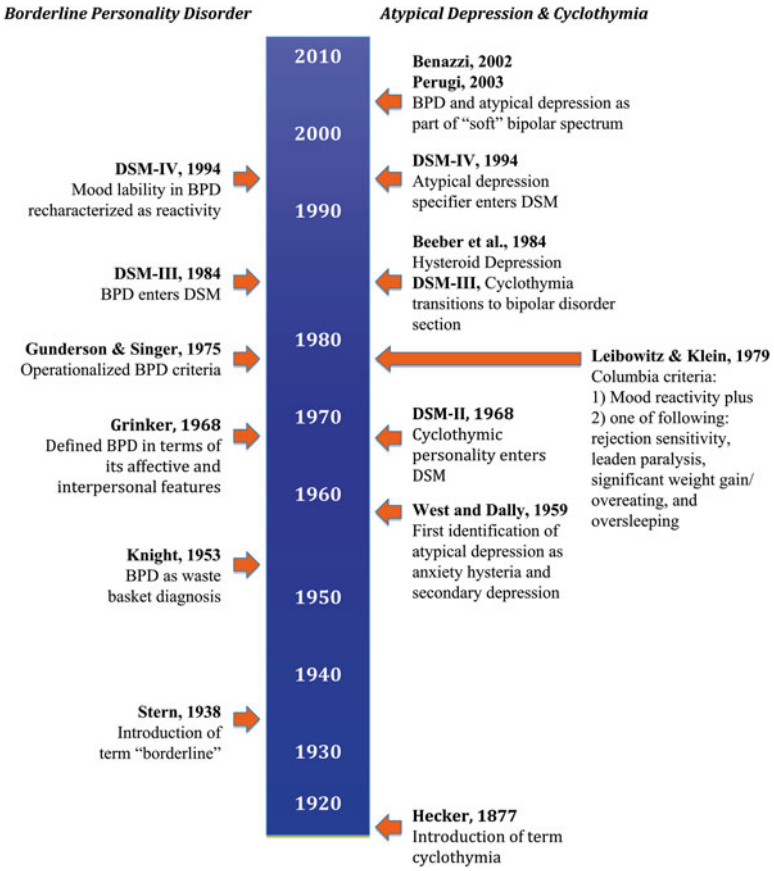

Fig. 3.2 History of borderline personality disorder, atypical depression, and cyclothymia diagnoses

atypical depression and BPD [21], but it has failed to be validated as a discrete diagnostic entity [22].

As the field of psychiatry moved away from psychoanalytic conceptualizations emphasizing phenomena such as hysteria, it began to focus heavily on descriptive approaches to defining psychiatric illnesses. During this time, the definition of atypically depressed patients became more focused on distinct symptoms rather than on personality. The diagnostic criteria later adopted in DSM-IV were formulated by the Columbia University mood disorders research group of Klein and collaborators to include: (1) the presence of mood reactivity (i.e., positive mood changes from positive life events) and (2) two or more of the following four symptoms: interpersonal rejection sensitivity, leaden paralysis, significant weight gain or overeating, and oversleeping [23, 24]. This revision of the diagnostic framework for atypical depression moved away from emphasizing anxiety and characterologic features connecting atypical depression to Cluster B disorders, instead focusing on mood reactivity as its cardinal feature.

As this conceptualization of atypical depression has been put to empirical test since its inclusion in the DSM-IV, its status as a valid mood disorder subtype has remained controversial [17]. Studies testing its diagnostic validity and coherence have proposed further revision to these criteria. Studies have challenged the primacy of mood reactivity, which demonstrates weak association to the other four accessory symptoms [17, 25, 26] indicating that anxiety [27, 28] and rejection sensitivity [29] are more empirically robust candidates as an organizing core feature of this distinctive atypical form of depression. Hyperphagia and hypersomnia have been conceptualized as compensatory or self-regulatory homeostatic responses to the depression to which rejection-sensitive individuals are prone [17, 30].

Parker has developed a conceptualization of atypical depression as a "multiaxial" diagnosis which spans both Axis I symptoms and Axis II personality features [31]. Using a "spectrum model," Parker argues that temperamental and personality characteristics—which include internalizing/anxious, externalizing/irritable, and volatile/self-focused types—interact with life stress to produce anxious, irritable, and hostile depressive phenotypes. Parker specifies atypical depression as a variant of depression co-occurring with "a personality style of sensitivity to rejection predisposing to a set of dysregulated emotional responses and self-consolatory strategies." According to Parker, inherent in this rejection sensitive personality are features of "(1) feeling abandoned, (2) feeling unable to rely on other people, (3) feeling rejected, (4) feeling lonely, and (5) crying" [31] which overlap with the interpersonal phenomenology of BPD. Parker's proposed model of the relationship between temperamental or personality features and different depression phenotypes provides a more coherent framework for understanding the interaction between the personality trait of rejection sensitivity and the acute variation on depressive symptoms represented in the atypical depression subtype.

A competing theory explaining the relationship between temperamental or personality-related factors and mood problems has been advanced by advocates arguing for the expansion of the bipolar spectrum. This theory postulates that cyclothymia is the underlying basis of atypical depression. Perugi et al. [13, 32] proposed that atypical depression may be most accurately located on the "soft" bipolar spectrum and that a cyclothymic diathesis may be the central characteristic that mediates mood lability in personality disorders such as BPD. Despite the failure of empirical investigations to validate mood reactivity as the central characteristic of atypical depression, advocates for the expansion of the bipolar spectrum have continued to presume its centrality to justify a bridge between this atypical variant of depression and bipolar disorder.

Cyclothymia

The history of the concept of cyclothymia extends to the beginning of the classification of psychiatric diseases [33–36]. Ewald Hecker, a student and close collaborator of Karl Kahlbaum, coined the term in 1898, when he defined cylcothymia as a

condition with fluctuations in mood between depressive and excited extremes, lasting as briefly as days in milder subthreshold mood states to longer episodes lasting weeks to months with more severe or full-blown presentations of depression and hypomania. Kahlbaum elaborated on Hecker's description, delineating the difference between this milder variant of cyclothymia and "circular typical insanity." According to Kahlbaum, cyclothymia could be considered a "partial disorder of the soul," with a favorable course even though it could last a lifetime and did not require treatment or hospitalization. In contrast, the more clinically serious form of cyclical insanity involved a course of alternating depressive and manic events, with a marked tendency towards deterioration and confusion [37]. Both Hecker's and Kahlbaum's early descriptions of cyclothymia distinguish it as a milder, ambulatory, constitutional feature that can develop into more full-fledged versions of bipolar illness. Kraepelin also positioned cyclothymia as a constitutional state predisposing individuals to frank manic-depressive illness, conceptualizing it on the milder, predisposing side of the bipolar spectrum [33].

Since its introduction into the psychiatric literature, the scope and utility of cyclothymia has remained unclear. In the early twentieth century, its critics argued it was too loosely applied and appeared to be a "wastebasket diagnosis" [34]. The boundaries between the constitutional subthreshold, and full-blown forms of manic-depressive illness remain blurred in the spectrum concept which claims a continuum between cyclothymic temperament, a normal variation on personality, and manic psychosis, a discrete pathological variation on mood. In the mid-twentieth century, Kurt Schneider argued against this spectrum concept of psychiatric disease, rejecting the notion that schizophrenia or manic-depression were rooted in a temperamental or personality-based diathesis [34, 38].

Amid the controversy about defining cyclothymia as either a personality variant predisposing individuals to bipolar disorder or as an episodic mood disorder, cyclothymia was introduced under the affective personalities section in the second edition of the DSM as a personality style alternating between depression, with features of "worry, pessimism, low energy, and a sense of futility," and elation, with features "ambitious, warmth, enthusiasm, optimism, and high energy" [39]. With the advent of antidepressant medications, a major paradigm shift occurred in understanding affective disorders, emphasizing the distinction between unipolar and bipolar illness over the distinctions between organic endogenous and neurotic reactive mood disorder variants [40, 41]. DSM-II diagnostic criteria were put to empirical test and found to lack reliability, catalyzing a reformulation of more empirically derived diagnostic criteria. The radical shift in therapeutics and diagnostics is reflected in the transition to DSM-III [42], where cyclothymia moved from classification as an affective personality to classification as a mood disorder [34].

Since its reclassification as a subthreshold form of bipolar disorder in the DSM-III, cyclothymia has had little clinical utility as a diagnostic entity [7, 35]. Most patients who present with subthreshold versions of bipolar disorder are commonly diagnosed as bipolar II, bipolar not otherwise specified, or with rapid cycling bipolar disorder. Since conversion into the DSM as a "Bipolar and Related Disorder," it has remained intact in terms of describing a mood disorder, but has continued to be

researched as a personality trait or temperament. Its use continues to vary as (1) a form of bipolar disorder independent of bipolar I and II, (2) a subthreshold and milder version of bipolar disorder, (3) an early variant or *forme fruste* that eventually evolves into bipolar disorder, and (4) a predisposing factor that influences vulnerability to both disorders [28]. Among the advocates for the concept of bipolar spectrum disorders, Hagop Akiskal argues that cyclothymia is both a lifelong trait and predisposition to bipolar spectrum variants as well as a discrete subsyndromal variant of bipolar disorder [34, 43]. In this dual definition, cyclothymia describes a trait, personality feature, or temperament, as well as a state or disorder, like a mood episode. Similar to atypical depression, cyclothymia has been defined in a way that has crossed diagnostic axes with both mood and personality features.

Borderline Personality Disorder

The term "borderline" was first introduced by Adolph Stern in 1938 [44] to describe a category of patients whose presentations defied classification as either psychotic or neurotic and therefore seemed to occupy a borderline between these major nosological domains. In his characterization of these patients, Stern described narcissism, psychic bleeding (i.e., low perseverance), inordinate hypersensitivity, psychic and body rigidity, constitutional feeling of inferiority, masochism, organic insecurity, projective mechanisms, and difficulties in reality testing. Stern also highlighted the tendency of these patients to have "negative therapeutic reactions," noting they were "extremely difficult to handle effectively by any psychotherapeutic method" [44]. In this initial description by Stern, borderline patients were distinguished by their poor fit with both prevailing diagnostic categories and existing therapeutic approaches. Parallel to the development of the atypical depression diagnosis, the discovery of the borderline group of patients occurred in the context of a poor response to usual treatments.

The confusion in defining the boundaries and overlaps between this group of borderline patients and those patients with neurotic and psychotic disorder is reflected in the variety of terms used to signify this clinical phenomenon. At first, borderline personality was defined at its psychotic borders, as a less severe variant of schizophrenia, with distinction as a form of ambulatory schizophrenia [45], pseudopsychopathic schizophrenia [46], or pseudoneurotic schizophrenia [47, 48]. While psychiatrists struggled to clarify the defining features of this borderline group of patients, what was notable about their presentations is that they were "stable in their instability" [49]. Robert Knight critically observed the lack of consistency in the various descriptions of these patients, noting the term borderline had become a "wastebasket" for patients whom psychiatrists were not able to classify as either purely psychotic or purely neurotic [50]. Despite Knight's criticism of the diagnosis, he noted that the failure to identify the particular needs of this patient group contributed to management conflicts and difficulties on inpatient units which arise out of a failure to appreciate the vulnerability these patients had to regress in unstructured environments.

In the 1960s, Otto Kernberg clarified the concept of *borderline personality organization,* distinguishing aspects of psychological functioning that characterized this group of patients. Kernberg outlined three key features of patients operating at a borderline level of personality, including (1) failed identity formation or identity diffusion, (2) primitive defenses (i.e., splitting and projective identification), and (3) stress-related lapses in reality testing which defined this level of personality functioning occupying the border between its more disturbed psychotic and more healthy neurotic counterparts [51]. The first formal study of borderline patients was published by Roy Grinker shortly thereafter, establishing an empirically derived criterion set which included (1) anger as the dominant affect, (2) impaired interpersonal relationships, (3) lack of self-identity, and (4) depression [52]. Grinker's description of the borderline syndrome defined the affective border between borderline and depressed patients by incorporating the characteristic interpersonal and identity dysfunction with an emphasis on anger as the dominant affect (rather than depression). In a synthesis of the literature, Gunderson and Singer proposed a more detailed set of criteria [53] which was later operationalized in a reliable structured interview [54]. The adaptation of Kernberg's concept of identity diffusion, Gunderson's criteria for BPD, was adopted into the DSM-III.

Since the inclusion of BPD into the DSM-III, the borderline construct has transformed from a type of personality organization with a psychoanalytic explanation [51] to a disorder [55] which in a medicalized paradigm connects it to specific etiological and therapeutic bases. After the publication of the DSM-III, a robust scientific literature has evolved to validate BPD as a reliable and discrete diagnostic entity, by more stringent standards set by Robins and Guze [56] for all psychiatric diagnoses [55, 57–59]. In the transition of the diagnostic criteria from DSM-III to DSM-IV, the affective instability described in BPD was changed from its characterization as mood lability—with shifts between depression, irritability, and anxiety—to *mood reactivity* marked by *intense episodic dysphoria.* This distinction in quality of mood instability in BPD both overlapped with the mood reactive, dysphoric quality of atypical depression and also clarified the distinction from bipolar disorder, where the mood instability was distinguished as *labile*.

During the last three decades, the stigmatization of the BPD diagnosis has been reduced by a growing empirical literature suggesting high rates of remission and low rates of relapse over 10 years [60, 61] as well as amenability to treatment by a variety of different manualized psychotherapeutic approaches [8, 55]. Furthermore, family and twin studies of BPD demonstrate a level of heritability between that of major depressive and bipolar disorders, suggesting a significant contribution of genetic and environmental factors to its development. These studies also report evidence that a single latent BPD factor organizes the affective, behavioral, cognitive, and interpersonal symptoms within the diagnosis [62, 63]. These findings confirm the integrity and biological basis of the BPD diagnosis.

In the development of the latest edition of the DSM, fierce controversy ensued over a radical plan to overhaul the existing system of personality disorder classification to further dimensionalize these disorders and to consider core personality

features in relevance to both normal functioning and psychiatric disorders rather than exclusively in terms of the pathological variants described as personality disorders [64, 65]. The movement to dimensionalize all psychiatric diagnoses was propelled by a recognition of significant co-occurrence among different diagnoses, difficulty defining a valid cutoff between normal and pathological variants, and tendency towards diagnosis of atypical or "not otherwise specified" presentations due to the failure of existing diagnoses to define clinically prevalent presentations [65]. Two main alternatives considered in revising the personality disorders section of the DSM-V proposed dimensional ratings of personality features using the five-factor model [66] versus a prototype model, using the Shedler-Westen Assessment Procedure (SWAP) [67, 68]. In a study testing these alternative procedures for diagnosing personality disorders against existing DSM-IV diagnostic criteria, clinicians demonstrated significant difficulty translating ratings from the FFM and SWAP into DSM diagnoses, especially in cases presenting with comorbidity [69]. Considering the hard-won empirical basis for the existing diagnostic criteria, comparative inadequacy of empirical support for a new system, and evidence of the significant difficulty clinicians would have in utilizing a dimensionalized system, the DSM-IV diagnostic criteria of all the personality disorders were retained without change. However, one significant change which occurred in the larger DSM-V revision was the elimination of the multiaxial system of diagnosis which suggested a false distinction between mental and medical illnesses as well as between Axis I and II disorders.

Despite the lack of adequate consensus and evidence for a more dimensionalized approach to the diagnosis of personality, there are important clinical and empirical benefits to considering broader underlying factors that determine the patterns of comorbidity we observe in these disorders. As noted throughout, the comorbidity of BPD with a variety of other psychiatric diagnoses is common [70], and multivariate methods have been applied to analyze the underlying structures that may determine the co-occurence of different disorders, suggesting that internalizing dimensions contribute to the pattern of comorbidity with unipolar mood and anxiety disorders, while externalizing dimensions contribute to comorbidity with disinhibitory disorders such as substance-related disorders and antisocial personality [71]. This movement to understand broader factors which underlie the complex comorbidity patterns may ultimately clarify the overlaps between mood and personality features. Furthermore, longitudinal studies have clarified distinctions between the more enduring stable affective and interpersonal traits of BPD—such as intolerance of aloneness and dependency—and more acute, reactive, and impulsive features of the illness such as self-destructive and suicidal acts [60]. This finding suggests a division between temperamental traits and stress-reactive symptom states within the BPD diagnosis. More research is needed to understand the core biological and temperamental traits which may predispose individuals to acute manifestations of BPD as well as other comorbidities that span the previously divided Axis I and II disorders.

Diagnostic and Empirical Overlaps

The diagnostic and clinical features of these three disorders overlap in terms of their early age of onset, female gender predominance, and chronicity. All three disorders also show high rates of comorbidity with anxiety, substance, eating, somaticization, and other personality disorders (Table 3.1). These clinical features suggest that patients who present with atypical depression, cyclothymia, and BPD will challenge clinicians to prioritize and organize treatment strategies that most broadly address key features of these overlapping disorders. Understanding the specific clinical overlapping features between these diagnoses can organize core components that may address multiple comorbidities with the most parsimonious treatment plan.

Table 3.1 Clinical overlaps atypical depression, cyclothymia, and borderline personality disorder [6, 11, 25, 31, 32, 35, 55, 60, 72]

	Atypical depression	Cyclothymia	Borderline personality disorder
Prevalence	15.7–36.6 % depressed patients [72]	4–6 % general population [35]	1.6–5.9 % general population [11]
Gender predominance	Female [25, 31]	Female [35]	Female [11]
Age onset	Adolescence [6]	Postpubertal [35]	Early adulthood [11]
Chronicity	Chronic, nonphasic [6]	Chronic, cyclic 1/3 experience affective episodes [35]	Chronic with high rates of remission over 10 years [11]
Comorbidity axis I			
	Panic disorder with agoraphobia 31.5 %	Panic disorder with agoraphobia 57.8 %	Depression 50 %
	Social phobia 54.6 %	Bulimia nervosa 26.7 %	Bipolar II disorder 11 %
	Hypochondriasis 5.4 %	Alcohol-related disorders 15.6 % [32]	Bipolar I disorder 9 %
	Body dysmorphic disorder 6.9 % [25]		Substance abuse 35 %
			Eating disorders 25 %
			PTSD 30 % [55]
Comorbidity axis II			
Borderline	10 %	62.2 %[b]	–
Narcissistic	1 %	27.3 %	16.4 %
Antisocial	0 %	–	22.7 %
Histrionic	1 %[a]	34.0 %	15.3 %
OCPD	6 %	40.9 %	18.2 %
Dependent	1 %	62.2 %[b]	50.7 %
Avoidant	23 %[a] [25]	56.8 % [32]	43.0 % [60]

[a] $p < 0.0015$
[b] $p < 0.05$

Table 3.2 Diagnostic overlaps atypical depression and borderline personality disorder [11]

Atypical depression (2 or more)	Borderline personality disorder (5 or more)
Mood reactivity	Affective instability (mood reactivity)
	Inappropriate and intense anger
Interpersonal rejection sensitivity	Frantic efforts to avoid abandonment
	Unstable and intense relationships
Increased appetite	Impulsivity
Hypersomnia	
Leaden paralysis	Chronic feelings of emptiness
	Identity disturbance
	Self-destructive and suicidal behavior
	Paranoid ideation or severe dissociative symptoms

Source: American Psychiatric Association [11]

Atypical Depression and BPD

The core features of atypical depression overlap completely with defining affective and interpersonal core features of BPD (Table 3.2). Individuals with either diagnosis present with mood reactivity, primarily influenced by interpersonal triggers such as rejection or abandonment. In the literature on atypical depression, this qualifier is often referred to as "paradoxical anhedonia," alluding to the distinction that these atypically depressed states are exogenously (as opposed to endogenously or biologically) determined. While formally required to meet the DSM diagnostic criteria for atypical depression, mood reactivity fails to show significant relationships to the other criteria within the diagnosis [17, 25]. For borderline patients, mood reactivity also refers to the generation of negative affects to stressful or negative environmental triggers or events. These environmental triggers are primarily interpersonal, but can include other types of life stress and typically precede impulsive or self-destructive acts [73, 74]. Similar to the dysphoric states observed in atypical depression, depressive states in BPD are prone to radical shifts if attachment figures previously seen as rejecting are then experienced as accepting [75, 76]. In contrast to the research findings pointing to the lack of relationship among the criteria for atypical depression, factor analytic studies of BPD suggest that the affective, behavioral, and interpersonal symptom sectors are interrelated [77–79]. Both affective dysregulation and interpersonal hypersensitivity have been hypothesized as core organizing features of BPD [80–82].

The criterion of interpersonal rejection sensitivity, describing pattern of anxious hypervigilance and angry reactivity towards real or perceived rejection [83], stands alone in terms of relationally based criterion in all of the mood disorder diagnoses, but is a core feature of a number of disorders (e.g., social anxiety, avoidant personality disorder) including BPD [84]. Rejection sensitivity was first incorporated into the diagnostic definition of atypical depression with two important distinguishing features: (1) a trait-like quality with persistence outside the

time frame of active depressive episodes and (2) a degree of relevant functional impairment, described in terms of "stormy relationships." Notably, this definition of rejection sensitivity was introduced into the atypical depression diagnostic criteria by a group of mood researchers at Columbia University, where the rejection sensitivity concept was later operationalized and studied as a psychological concept separate from a diagnostic entity [83]. In its development, rejection sensitivity was associated with a pattern of behavioral reactivity, such as leaving work early and substance use [6].

In BPD, interpersonal rejection may be a prototypical trigger to both affective (anxious and angry) and behavioral (substance abuse) components of the disorder. The specific sensitivity of individuals with BPD to rejection has been documented both empirically and phenomenologically [84–86]. Some experts have theorized IRS as a core trait of individuals with BPD, advocating for its inclusion into a revised diagnostic description of BPD [87]. While mood reactivity is the required criteria for the diagnosis of atypical depression, more recent research suggests IRS as a more defining clinical feature both atypical depression and BPD [31].

The reversed neurovegetative symptoms (i.e., hypersomnia and hyperphagia) and leaden paralysis, while not diagnostic of BPD, are highly characteristic of behavioral and psychosomatic aspects of individuals with the disorder. Impulsive symptoms in BPD are often conceptualized in terms of solutions to or avoidance of emotional distress. Oversleeping and overeating function as behavioral responses, which serve to distract from or enable avoidance of painful emotional intensity for BPD patients. These symptoms have also been characterized as compensatory and reactive in atypical depression [17]. Leaden paralysis, defined as the tendency to feel heavy, weighed down, and paralyzed for at least 1 h a day at least three times weekly, has been re-characterized within the atypical depression literature as lethargy and fatigue [17]. Recent research suggests it may not be a feature that distinguishes atypically depressed patients from those with other forms of depression. Chronic fatigue has been associated with BPD [4], and both may be connected with beliefs about negative emotions as unacceptable [88].

Very little scientific literature exists to clarify the relationship between these two diagnostic entities, despite the clear overlaps in clinical features. In studying the types of depression in BPD, Soloff and collaborators reported that 16 of 39 inpatients with BPD met criteria for atypical depression (41 %), and 25 of 29 (64.1 %) met criteria for hysteroid depression [89]. While a majority of borderline patients met criteria for atypical variants of depressive disorders, no one form of depression seemed to capture the depressive features in BPD accurately [89]. In a much larger study by Posternack and Zimmerman of 579 psychiatric outpatients with major depression, subjects with atypical depression demonstrated higher ratings on the traits for all DSM-IV Personality Disorders when compared with patients with non-atypical depression, but only traits scores for histrionic and avoidant personality were higher at a statistically significant level for patients with atypical depression compared to non-atypical depression. Scores on borderline and narcissistic traits were reported as higher in the atypically depressed subjects compared to the non-atypically depressed subjects, but these differences were not significant once

Bonferroni correction was applied [25]. Lastly, a study by Perugi and colleagues assessed 107 ambulatory (partial hospital and outpatient) subjects with atypical depression [32], finding a large proportion of these subjects met criteria for various personality disorders including histrionic (25.2 %), narcissistic (18.7 %), obsessive-compulsive (38.3 %), dependent (46.7 %), avoidant (60.7 %), and borderline (37.4 %) personality disorders [32]. Like in the Posternack and Zimmerman study, avoidant personality disorder, not BPD, was most common among atypically depressed patients. Interpersonal rejection sensitivity and separation anxiety are two features that avoidant, dependent, and borderline personality disorders have in common with atypical depression [13].

This limited literature suggests that several personality disorders may have important overlaps with atypical depression, especially avoidant personality, but that the majority of individuals with atypical depression do not have BPD and the majority of individuals with BPD do not have atypical depression. The construct of atypical depression arose to delineate a group of specific patients with interpersonal sensitivities, mood reactivity, and differential response to medications, but the empirical literature has failed to validate it as a coherent diagnostic concept. Overtime, the definition and conceptualization of atypical depression has become overextended to a point that its construct validity has been questioned [90]. It is likely that patients captured under this rubric of atypical mood presentation really represent heterogeneous patients with complex presentations associated with a variety of types of character pathology, including BPD. The atypical depression diagnosis importantly indicates the likelihood of a co-occurring personality disorder which relates to a more interpersonally reactive, dysphoric variant of depression with behavioral symptoms that may be triggered by either rejection or the dysphoric reactions to rejection experienced by these patients. This form of depression is not likely to respond to usual treatments. In contrast, the diagnosis of BPD has been robustly validated as a coherent clinical entity encompassing the wide range of interpersonally sensitive, emotionally dysregulated, and behaviorally and cognitively dyscontrolled symptoms and lends itself to a wide range of specific validated therapeutic interventions.

Cyclothymic Temperament and BPD

As a temperamental trait, cyclothymia is expressed by fluctuations between (1) hypersomnia and decreased need for sleep, (2) introverted self-absorption and disinhibited gregariousness, (3) taciturn and talkative behaviors, (4) unexplained tearfulness and buoyant jocularity, (5) psychomotor inertia and restless pursuit of activity, (6) lethargy/somatic discomfort and eutonia, (7) dulling of the senses and keen perceptions, (8) slow-witted and sharpened thinking, (9) low self-esteem and overconfidence, and finally (10) pessimistic brooding and optimistic, carefree attitudes (Table 3.3) [91]. Cyclothymia is hypothesized to be the dispositional core of affective dysregulation [91], a putative underlying mechanism behind both

Table 3.3 Cyclothymic temperament (*3 out of 5 from both sets*) [32]

3 out of 5		
Hypersomnia		Decreased need for sleep
Introverted self-absorption		Uninhibited people-seeking
Taciturn		Talkative
Unexplained tearfulness		Buoyant jocularity
Psychomotor inertia		Restless pursuit of activities
3 out of 5		
Lethargy and somatic		Eutonia
Discomfort		Keen perceptions
Dulling of senses		Sharpened thinking
Slow witted		Overconfidence
Low self-confidence		Optimism/carefree attitude
Pessimistic brooding		

Biphasic dysregulation characterized by sudden and "endoreactive" shifts, with each phase lasting a few days at a time. Onset in late adolescence and early adulthood

bipolar [43, 92] and borderline personality disorders [80]. In identifying the cyclothymic temperament, Akiskal claimed that different phases of the shifting presentation of cyclothymia can illicit "emotional avalanches" in response to "trivial interpersonal stress," which are then followed by depressive lows [91]. This type of affective intensity and the related behavioral tendencies described by Akiskal can routinely undermine an individual's relational stability in both romantic and professional realms. Ultimately the distinctions between cyclothymic temperament and BPD are not clear, but the clinical overlaps between the interpersonal sensitivity and mood reactivity in cyclothymia, atypical depression, and BPD suggest that patients with these two features will be variably diagnosed and treated.

Many patients with BPD could easily fulfill criteria for cyclothymia given the sensitivity of their mood and behavioral reactivity interpersonal contexts. However, individuals with BPD are not characteristically elated like bipolar II or cyclothymic individuals [93] but rather are commonly characterized as irritable, angry, and dysphoric. Akiskal has justified that in BPD "sunnier" sides of cyclothymia are obscured because "dysphoria pervades their short-lived periods of excitement" [94].

Very little scientific literature exists to scientifically quantify the diagnostic overlaps between cyclothymia and BPD. Two studies have reported on the prevalence of cyclothymia in BPD [13, 32, 95]. In the first of these studies, 60 patients with personality disorders were evaluated for cyclothymia [95]. Levitt and collaborators found that while cyclothymia was more common in BPD subjects compared to subjects with other personality disorders (OPD) in this small study, the distinction between cyclothymic and non-cyclothymic borderline subjects was not related to any behavioral or functional differences. Furthermore, the prevalence of different forms of mood disorders was not statistically different between the BPD and OPD

groups [95]. The second study on cyclothymia and BPD reported by Perugi and colleagues divided patients into cyclothymic ($n=45$) versus non-cyclothymic groups ($n=62$) [32] and also into BPD ($n=46$) and non-BPD groups ($n=61$) [13]. In this study, a majority of subjects with both atypical depression and cyclothymia also met criteria for BPD (62.2 %) [32], and a majority of subjects with atypical depression and BPD met criteria for cyclothymia (58.7 %) [13]. Compared to non-cyclothymic subjects, cyclothymic subjects with atypical depression were also more likely to have panic disorder with agoraphobia, bulimia nervosa, and alcohol-related disorders [32]. When BPD and non-BPD subjects with atypical depression were compared, those with BPD had greater likelihood of comorbidity with recurrent major depression, body dysmorphic disorders, bulimia nervosa, narcissistic personality, dependent personality, and avoidant personality than their non-BPD counterparts [13], suggesting atypically depressed patients with BPD or cyclothymia presented with a more complex clinical presentation involving diagnoses spanning the anxiety, behavioral, substance use, and personality disorder realms. This finding is consistent with prevailing notions that individuals with BPD present with a usual complex pattern of comorbidity that challenges the general mental health clinician in developing a coherent and effective treatment [70].

Perugi and his collaborators argue that the presence of cyclothymia in patients with atypical depression and BPD seems to explain most of the relationship between these two disorders [13]. In their study, cyclothymic temperament contributed significantly to 6 out of 9 BPD criteria in patients with atypical depression, including frantic efforts to avoid abandonment, unstable relationships, identity disturbances, impulsivity, self-destructive tendencies, affective instability, and chronic feelings of emptiness. The two criteria for which cyclothymia did not contribute significantly were inappropriate, intense anger and transient stress-related paranoia/dissociation [13]. In this study, cyclothymia was empirically associated with more BPD criteria than dependent, avoidant, histrionic, or narcissistic personality disorder or any other affective temperament.

While Perugi and colleagues explain that the overlap between atypical depression and BPD is accounted for by cyclothymia, there are other possible explanations for these overlaps. Empirically, atypical depression, cyclothymia, and BPD overlap in features of interpersonal sensitivity and mood reactivity; however, interpersonal sensitivity is only empirically associated with cyclothymia, which is conceptualized more specifically as a mood lability. Both atypical depression and BPD are both empirically and theoretically organized around core interpersonal vulnerabilities. Limited research suggests attachment anxiety appears to be an underlying feature that increases vulnerability to negative affective temperaments (i.e., dysthymic and cyclothymic) and personality disorders in general as well as BPD specifically [96]. Whether interpersonal sensitivity is inherent to cyclothymia or a commonly co-occurring factor which interacts with cyclothymia to increase risk for atypical depression and/or BPD requires further study.

Treatment Overlaps

Proper treatment for any psychiatric illness starts with proper diagnosis. As noted in the consideration of the diagnostic overlaps and tendencies towards comorbidity between atypical depression, cyclothymia, and BPD, deciding on a proper primary diagnosis is challenging at best. From the limited research on the co-occurrence of these disorders, it is clear that many patients with atypical depression will have both BPD and cyclothymia, and those patients will likely present with more complex clinical pictures.

For those who favor psychopharmacologic approaches, medication management will present a number of challenges. While atypical depression was first distinguished in terms of its specific responsiveness to MAOI agents over TCAs, the replication of these findings is variable and seems to suggest a decreased responsiveness to TCA rather than an increased responsiveness to MAOIs (see Rabkin et al. [6] for review). Some evidence exists demonstrating interpersonal sensitivity is correlated to responsivity to the MAOI medication [27]. In the modern (post-MAOI) age of psychopharmacology, few adequately powered studies have examined the efficacy of safer drugs, like SSRIs, on atypical depression [97]. The newer transdermal formulation of MAOI selegiline may offer some practical advantages in the elimination of dietary restrictions at lower doses, but no studies on the efficacy of this formulation on atypical depression have been published to date. Lastly, while there is a dearth of research on psychotherapeutic interventions for atypical depressions, existing literature has suggested the efficacy of cognitive behavioral interventions for atypical depression, with higher retention of patients when compared to treatment by MAOI [97, 98].

In general, medications are not adequate as a primary intervention strategy for BPD [99, 100, Silk this volume]. Antidepressants show limited efficacy for depressive and anxious symptoms in BPD [99] unless there is a co-occurring major mood disorder. BPD and major depressive disorder are highly comorbid, and research examining the longitudinal course of these disorders suggests that the remission of MDD will be significantly slowed in the presence of BPD [101]. Some reports suggest the efficacy of MAOIs for patients with both atypical depression and BPD [102, 103], while other reports suggested that MAOIs reduced symptoms of anger and hostility in BPD but did not demonstrate significant efficacy for treating symptoms of atypical depression or hysteroid dysphoria in patients with BPD [103].

These findings are of interest in the context of more recent functional imaging and genetic studies that suggest a genetic polymorphism with lower expression of the MAO-A gene is associated with increased self-reported interpersonal hypersensitivity and aggression as well as increased dorsal anterior cingulated activity in a social exclusion task [104]. These findings imply that there may be a MAO-based genetic endowment that contributes to traits of rejection sensitivity and aggression in individuals that might have BPD and/or atypical depression. More research is needed to study changes in interpersonal sensitivity specifically in response to

MAO-active medications, but the existing literature on the efficacy of these agents on BPD and atypical depression is mixed at best.

The implication of MAOIs as a potentially effective pharmacologic intervention is complicated also by practical concerns around lethal food and drug interactions in a highly impulsive and suicidal category of patients. Patients with both atypical depression and BPD have higher rates of suicidality during acute presentations than those without BPD [13]. The risk of intentional and unintentional overdose or toxic combination of medication is therefore increased for this group of patients, rendering the administration of MAOI agents complicated. While newer transdermal formulations may be safer, they have not been tested to date in this particular population, and researchers may not pursue such studies given the risk. These safer formulations are expensive and will likely remain unavailable to many patients who have not failed extensive adequate trials of other medications, since studies supporting its indication in treatment for atypical depression and BPD are lacking.

The trend towards inclusion of atypical depression (with or without BPD) in the bipolar spectrum further complicates treatment considerations, since the role of antidepressants in switching patients into mania may then limit their safety for this group of patients. Furthermore, while lithium has shown some efficacy in patients with cyclothymia [7, 105–107], lithium has shown limited efficacy for hostile and impulsive features of BPD [108] and can be both toxic in side effects and lethal in overdose for BPD patients.

The research literature on the treatment of cyclothymia distinct from bipolar disorder is limited. Most of this small body of research focuses on the treatment of cyclothymia in its DSM-IV definition as a mood disorder rather than a temperament. Even for the DSM-defined disorder cyclothymia, there are no blinded randomized clinical trials for pharmacologic interventions, but some studies suggest that cyclothymia and other forms of bipolar disorder respond similarly to mood-stabilizing and antipsychotic agents [7, 109]. Only a handful of small studies examining the efficacy of cognitive behavioral therapy for cyclothymia have been published, demonstrating efficacy in reduction in mood and anxiety symptoms [7, 110].

The medications of choice given the overlaps between these disorders might concentrate on anticonvulsant mood stabilizers lamotrigine and topiramate and low-dose atypical antipsychotics [111]. These medications demonstrate the safest side effect profile and highest efficacy for patients with anxiety as well as mood instability, impulsivity, and psychotic-like symptoms which occur in both bipolar disorders and BPD. Medications with more toxic side effect profiles and lethality in overdose, like MAOIs, lithium, and valproate, may be indicated only in situations where other treatment options, including psychotherapy, have been attempted and failed or under conditions of supervised medication administration (i.e., longer-term intensive levels of care).

Psychotherapeutic approaches prevail as the intervention of choice for the affective instability and relational problems inherent in BPD. There are a number of empirically validated manualized psychotherapies for BPD (see chapters by Jacob

and Rodriguez-Villa and Luyten and Fonagy) which vary in their focus on affective instability (i.e., Dialectical Behavioral Therapy [77] or Cognitive Behavioral Therapy [112, 113]) versus interpersonal sensitivity (i.e., Mentalization-Based Treatment [114]; Transference-Focused Therapy [115]). All these treatments may more directly ameliorate or manage long-standing personality traits that lie at the core of these three disorders. While no drug studies demonstrate long-term stability of gains in patients treated with any of these three disorders, studies of these psychotherapeutic approaches in BPD show the stability and continuation of gains as long as 2–8 years after treatment [116, 117]. While more research is needed to compare the longer-term efficacy of both psychopharmacologic and psychotherapeutic approaches on symptomatic improvement and functioning, the current literature favors psychotherapeutic approaches as more definitive long-term treatments for patients with BPD.

One of the major problems with psychotherapeutic approaches is the lack of availability of these specialized treatments to the general population. The training for these empirically validated manualized treatments for BPD is expensive and exclusively offered through specific institutions and organizations. In recognition of this problem, more research and education has been devoted to developing more generalist psychiatric approaches to managing BPD. One of these manualized approaches, called General Psychiatric Management (GPM), has been proven to be as effective as DBT [118] with sustained clinical improvement in depressive symptoms, self-destructive behaviors, and interpersonal functioning [119]. The formulation of BPD organizing GPM focuses on the influence of the core of interpersonal hypersensitivity in the varied and fluctuating symptomatic presentations of patients with the diagnosis. This trend towards less intensive generalist approaches to BPD treatment may expand the availability of effective treatment for patients with BPD. GPM's focus on interpersonal sensitivity may address the common relational vulnerabilities seen in atypical depression, cyclothymia, and BPD, and contribute to the effective management of these overlapping disorders.

The evidence basis for psychotherapeutic interventions for both atypical depression and cyclothymia is preliminary and limited. A few studies have indicated the efficacy of cognitive behavioral approaches for both disorders [7, 95, 110]. Traditional cognitive behavioral approaches tend to target anxious, affective, and behavioral symptoms primarily, not interpersonal vulnerabilities. While a general cognitive behavioral psychotherapeutic approach may be easier to administer in a general psychiatric setting for patients with a wider range of diagnoses, it may be less effective than specific approaches developed to treat these patients whose diagnostic designations were associated with poor treatment response to general approaches that do not address the particular interpersonal features of these patients. More research is needed to assess the applicability of these BPD-specific psychotherapeutic approaches for atypical depression and cyclothymia.

Conclusions

This chapter reviewed the existing and limited literature examining the overlap between atypical depression, cyclothymia, and BPD. The clinical similarities (see Table 3.3) between these groups in terms of female preponderance, early age of onset, chronicity, complex pattern of comorbidity, and resistance to usual treatments often confuse clinicians, who may be prone to misdiagnose patients and manage their treatments erratically given the lack of well-studied, practical, tolerable, or available treatments for these patients. This diagnostic confusion as well as unclear treatment pathways contribute to the tendency for clinicians to approach these complex patients with pessimism or aim to avoid them altogether.

However, upon examination of core and common features which seem to organize shared manifestations of these different disorders, we can see that the mood-reactive and interpersonally sensitive temperamental endowments may determine the liability individuals have to all three of these disorders. While further research is needed to understand both the biology of and effective treatment approaches for the interpersonal rejection sensitivity observed in these diagnoses, theoretical and empirical rationale exist for the use of both MAOI medications and psychosocial treatments such as MBT and GPM. Additionally, the affective instability in cyclothymia and BPD may respond to pharmacologic approaches using mood stabilizers and atypical antipsychotics as well as cognitive behavioral psychotherapies, including DBT. Determining the predominant symptom profile—that is either interpersonally sensitive or mood reactive—may help clinicians choose a rationally and empirically based approach to these complicated patients. The limitation to these treatment guidelines is that (1) the medications indicated may present a significant liability in terms of side effects and lethality in overdose and (2) the psychotherapies indicated may not be readily available. Further efforts to expand research to clarify practical treatment approaches to managing these patients and proliferate the availability of these treatments are needed.

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References

1. Bassett D. Borderline personality disorder and bipolar affective disorder. Spectra of spectre? A review. Aust N Z J Psychiatry. 2012;46:327–39.
2. Vorma H, Naukkarinen HH, Sama SJ, Kuoppasalmi KI. Predictors of benzodiazepine discontinuation in subjects manifesting complicated dependence. Subst Use Misuse. 2005;40(4):499–510.
3. Frankenburg FR, Zanarini MC. Personality disorders and medical comorbidity. Curr Opin Psychiatry. 2006;19(4):428–31.

4. Frankenburg FR, Zanarini MC. Obesity and obesity-related illnesses in borderline patients. J Pers Disord. 2006;20(1):71–80.
5. Baldessarini RJ, Vieta E, Calabrese JR, Tohen M, Bowden CL. Bipolar depression: overview and commentary. Harv Rev Psychiatry. 2010;18(3):143–57.
6. Rabkin JG, Stewart JW, Quitkin FM, McGrath PJ, Harrison WM, Klein DF. Should atypical depression be included in DSM-IV. In: Widiger TA, Frances AJ, Pincus HA, Ross R, First MB, Davis WW, editors. DSM-IV sourcebook. Washington, DC: American Psychiatric Association; 1996.
7. Baldessarini RJ, Vazquez G, Tondo L. Treatment of cyclothymic disorder: commentary. Psychother Psychosom. 2011;80(3):131–5.
8. Gabbard GO. Do all roads lead to Rome? New finding on borderline personality disorder. Am J Psychiatry. 2007;164(6):853–5.
9. Bateman AW. Treating borderline personality disorder in clinical practice. Am J Psychiatry. 2012;169(6):560–3.
10. Akiskal H, Chen SE, Davis GC, Puzantian VR, Kashgarian MM, Bolinger JM. Borderline: an adjective in search of a noun. J Clin Psychiatry. 1985;46(2):41–8.
11. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington: American Psychiatric Publishing; 2013.
12. Akiskal HS. Delineating irritable and hyperthymic variants of the cyclothymic temperament. J Pers Disord. 1992;6(4):4.
13. Perugi G, Fornaro M, Akiskal AS. Are atypical depression, borderline personality disorder and bipolar II disorder overlapping manifestations of a core cyclothymic diathesis? World Psychiatry. 2011;10(1):45–51.
14. West ED, Dally PJ. Effects of iproniazid in depressive syndromes. Br Med J. 1959;1(5136): 1491–4.
15. Sargant W. Some newer drugs in the treatment of depression and their relation to other somatic treatments. Psychosomatics. 1960;1(1):14–7.
16. Sargant WW, Slater E. An introduction to physical methods of treatment in psychiatry. New York: Science House; 1972.
17. Parker G, Roy K, Mitchell P, Wilhelm K, Malhi G, Hadzi-Pavlovic D. Atypical depression: a reappraisal. Am J Psychiatry. 2002;159(9):1470–9.
18. Klein DF, Davis JM. Diagnosis and drug treatment of psychiatric disorders. Baltimore: Williams & Wilkins; 1969.
19. Liebowitz MR, Klein DF. Hysteroid dysphoria. Psychiatr Clin North Am. 1979;2:555–75.
20. Beeber A, Kline M, Pies R, Manring J. Hysteroid dysphoria in depressed inpatients. J Clin Psychiatry. 1984;45(4):164–6.
21. Liebowitz MR, Klein DF. Interrelationship of hysteroid dysphoria and borderline personality disorder. Psychiatr Clin North Am. 1981;4(1):67–87.
22. Spitzer RL, Williams JB. Hysteroid dysphoria: an unsuccessful attempt to demonstrate its syndromal validity. Am J Psychiatry. 1982;139(10):1286–91.
23. Stewart JW, McGrath PJ, Rabkin JG, Quitkin FM. Atypical depression. A valid clinical entity? Psychiatr Clin North Am. 1993;16(3):479–95.
24. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association; 1994.
25. Posternack MA, Zimmerman M. Partial validation of the atypical features subtype of major depressive disorder. Arch Gen Psychiatry. 2002;59:70–6.
26. Seemüller F, Riedel M, Wickelmaier F, Adli M, Mundt C, Marneros A, et al. Atypical symptoms in hospitalised patients with major depressive episode: frequency, clinical characteristics, and internal validity. J Affect Disord. 2008;108(3):271–8.
27. Davidson J, Miller R, Turnbull C, Sullivan JL. Atypical depression. Arch Gen Psychiatry. 1982;39(5):527–34.
28. Parker G, McCraw S, Fletcher K. Cyclothymia. Depress Anxiety. 2012;29(6):487–94.

29. Joyce PR, Mulder R, McKenzie JM, Luty SE, Cloninger CR. Atypical depression, atypical temperament and a differential antidepressant response to fluoxetine and nortriptyline. Depress Anxiety. 2004;19(3):180–6.
30. Thase ME, Frank E, Kornstein SG, Yonkers KA. Gender differences in response to treatment for depression. In: Frank E, editor. Gender and its effects on psychopathology. Washington, DC: American Psychiatric Press; 2000.
31. Parker GB, Thase ME. Atypical depression: a valid subtype? J Clin Psychiatry. 2007; 68(S3):e08.
32. Perugi G, Toni C, Travierso MC, Akiskal HS. The role of cyclothymia in atypical depression: toward a data-based reconceptualization of the borderline-bipolar II connection. J Affect Disord. 2003;73(1–2):87–98.
33. Kraeplin E, editor. Manic-depressive insanity and paranoia. Edinburgh: ES Livingstone; 1921.
34. Brieger P, Marneros A. Dysthymia and cyclothymia: historical origins and contemporary development. J Affect Disord. 1997;45(3):117–26.
35. Akiskal HS. Dysthymia and cyclothymia in psychiatric practice a century after Kraepelin. J Affect Disord. 2001;62(1–2):17–31.
36. Koukopoulus A. Ewald Hecker's description of cyclothymia as a cyclical mood disorder: its relevance to the modern concept of bipolar II. J Affect Disord. 2003;73(1–2):199–205.
37. Kahlbaum KL. Ueber cyklisches Irresein. Der Irrenfreund. 1882;24:145–57.
38. Schneider K. Psychopathic personalities. Springfield: Charles C. Thomas; 1958.
39. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 2nd ed. Washington, DC: American Psychiatric Association; 1968.
40. Angst J. On the etiology and nosology of endogenous depressive psychoses. A genetic, sociologic and clinical study. Monogr Gesamtgeb Neurol Psychiatr. 1966;112(1):1–118.
41. Perris C, d'Elia G. A Study of bipolar (manic-depressive) and unipolar recurrent depressive psychoses. X. Morality, suicide and life-cycles. Acta Psychiatr Scand. 1966;194:172–89.
42. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 3rd ed. Washington, DC: American Psychiatric Association; 1984.
43. Akiskal HS. The prevalent clinical spectrum of bipolar disorders: beyond DSM-IV. J Clin Psychopharmacol. 1996;16(2S):4S–14.
44. Stern A. Psychoanalytic investigation of and therapy in the border line group of neuroses. Psychoanal Q. 1938;7(4):467–89.
45. Zilboorg G. Ambulatory schizophrenia. Psychiatry. 1941;4:149–55.
46. Peterson DR. The diagnosis of subclinical schizophrenia. J Consult Psychol. 1954;18(3): 198–200.
47. Hoch P, Cattell J. The diagnosis of pseudoneurotic schizophrenia. Psychiatr Q. 1959;33: 17–43.
48. Hoch P, Polatin P. Pseudoneurotic forms of schizophrenia. Psychiatr Q. 1949;23(2):248–76.
49. Schmideberg M. The treatment of psychopaths and borderline patients. Am J Psychother. 1947;1(1):45–70.
50. Knight R. Borderline states. Bull Menninger Clin. 1953;17(1):1–12.
51. Kernberg O. Borderline personality organization. J Am Psychoanal Assoc. 1967;15(3): 641–85.
52. Grinker RR, Werble B, Drye R. The borderline syndrome. New York: Basic Books; 1968.
53. Gunderson JG, Singer MT. Defining borderline patients: an overview. Am J Psychiatry. 1975;132(1):1–10.
54. Gunderson JG, Kolb JE. Discriminating features of borderline patients. Am J Psychiatry. 1978;135(7):792–6.
55. Gunderson JG, Links PS. Borderline personality disorder: a clinical guide. Washington, DC: American Psychiatric Publishing; 2008.
56. Robins E, Guze SB. Establishment of diagnostic validity in psychiatric illness: its application to schizophrenia. Am J Psychiatry. 1970;126(7):983–7.

57. Gunderson JG. Borderline personality disorder: ontogeny of a diagnosis. Am J Psychiatry. 2009;166(5):530–9.
58. Skodol AE, Siever LJ, Livesley WJ, Gunderson JG, Pfohl B, Widiger TA. The borderline diagnosis II: biology, genetics, and clinical course. Biol Psychiatry. 2002;51(12):951–63.
59. Skodol AE, Gunderson JG, Pfohl B, Widiger TA, Livesely WJ, Siever LJ. The borderline diagnosis I: psychopathology, comorbidity, and personality structure. Biol Psychiatry. 2002;51(12):936–50.
60. Zanarini MC, Frankenburg FR, Reich DB, Silk KR, Hudson JI, McSweeney LB. The subsyndromal phenomenology of borderline personality disorder: a 10-year follow-up study. Am J Psychiatry. 2007;164(6):929–35.
61. Gunderson JG, Stout RL, McGlashan TH, Shea MT, Morey LC, Grilo CM, et al. Ten-year course of borderline personality disorder: psychopathology and function from the Collaborative Longitudinal Personality Disorders study. Arch Gen Psychiatry. 2011;68(8):827–37.
62. Gunderson JG, Zanarini MC, Choi-Kain LW, Mitchell KS, Jang KL, Hudson JI. Family study of borderline personality disorder and its sectors of psychopathology. Arch Gen Psychiatry. 2011;68(7):753–62.
63. Distel MA, Willemsen G, Ligthar L, Derom CA, Martin NG, Meale MC, et al. Genetic covariance structure of the four main features of borderline personality disorder. J Pers Disord. 2010;24(4):427–44.
64. Widiger TA, Lowe JR. A dimensional model of personality disorder: proposal for DSM-V. Psychiatr Clin North Am. 2008;31(3):363–78.
65. Skodol AE, Bender DS. The future of personality disorders in DSM-V? Am J Psychiatry. 2009;166(4):388–91.
66. Costa PTJ, McCrae RR. Revised NEO personality inventory: professional manual (NEO-PI-R). Odessa: Psychological Assessment Resources; 1992.
67. Shedler J, Westen D. Dimensions of personality pathology: an alternative to the five-factor model. Am J Psychiatry. 2004;161(10):1743–54.
68. American Psychiatric Association. Personality and personality disorders. Washington, DC: American Psychiatric Association; 2010.
69. Rottman BM, Ahn W, Sanislow CA, Kim NS. Can clinicians recognize DSM-IV personality disorders from five-factor model descriptions of patient cases? Am J Psychiatry. 2009;166(4):427–33.
70. Zanarini MC, Frankenburg FR, Dubo E, Sickel A, Trikha A, Levin A, et al. Axis I comorbidity of borderline personality disorder. Am J Psychiatry. 1998;155(12):1733–9.
71. Eaton NR, Krueger RF, Keyes KM, Skodol AE, Markon KE, Grant BF, et al. Borderline personality disorder co-morbidity: relationship to the internalizing-externalizing structure of common mental disorders. Psychol Med. 2011;41(5):1041–50.
72. Cristancho MA, O'Reardon JP, Thase ME. Atypical depression in the 21st century: diagnostic and treatment issues. Psychiatr Times. 2011;28(1):42–47.
73. Yen S, Pagano ME, Shea M, Grilo CM, Gunderson JG, Skodol AE, et al. Recent life events preceding suicide attempts in a personality disorder sample: findings from the collaborative longitudinal personality disorders study. J Consult Clin Psychol. 2005;73(1):99–105.
74. Brodsky BS, Groves SA, Oquendo MA, Mann JJ, Stanley B. Interpersonal precipitants and suicide attempts in borderline personality disorder. Suicide Life Threat Behav. 2006;36(3):313–22.
75. Westen D, Moses J, Silk KR, Lohr NE, Cohen R, Segal H. Quality of depressive experience in borderline personality disorders: when depression is not just depression. J Pers Disord. 1992;6(4):382–93.
76. Silk KR. The quality of depression in borderline personality disorder and the diagnostic process. J Pers Disord. 2010;24(1):25–37.
77. Fossati A, Maffei C, Bagnato M, Donati D, Namia C, Novella L. Latent structure analysis of DSM-IV borderline personality disorder criteria. Compr Psychiatry. 1999;40(1):72–9.

78. Sanislow CA, Grilo CM, McGlashan TH. Factor analysis of the DSM-III-R borderline personality disorder criteria in psychiatric inpatients. Am J Psychiatry. 2000;157(10):1629–33.
79. Clifton A, Pilkonis PA. Evidence for a single latent class of Diagnostic and Statistical Manual of Mental Disorders borderline personality pathology. Compr Psychiatry. 2007;48(1):70–8.
80. Linehan M. Cognitive-behavioral treatment of borderline personality disorder. New York: Guilford Press; 1993.
81. Gunderson JG, Lyons-Ruth K. BPD's interpersonal hypersensitivity phenotype: a gene-environment-developmental model. J Pers Disord. 2008;22(1):22–41.
82. Gunderson JG. Disturbed relationships as a phenotype for borderline personality disorder. Am J Psychiatry. 2007;164(11):1637–40.
83. Downey G, Feldman SI. Implications of rejection sensitivity for intimate relationships. J Pers Soc Psychol. 1996;70(6):1327–43.
84. Staebler K, Helbing E, Rosenbach C, Renneberg B. Rejection sensitivity and borderline personality disorder. Clin Psychol Psychother. 2011;18(4):275–83.
85. Berenson KR, Downey G, Rafaeli E, Coifman KG, Paguin NL. The rejection-rage contingency in borderline personality disorder. J Abnorm Psychol. 2011;120(3):681–90.
86. Miano A, Fertuck EA, Arntz A, Stanley B. Rejection sensitivity is a mediator between borderline personality disorder features and facial trait appraisal. J Pers Disord. 2013;27(4): 442–56.
87. Gunderson JG. Revising the borderline diagnosis for DSM-V: an alternative proposal. J Pers Disord. 2010;24(6):694–708.
88. Rimes KA, Chalder T. The Beliefs about Emotions Scale: validity, reliability and sensitivity to change. J Psychosom Res. 2010;68(3):285–92.
89. Soloff PH, George A, Nathan RS, Schulz PM. Characterizing depression in borderline patients. J Clin Psychiatry. 1987;48(4):155–7.
90. Ohmae S. The modern concept of atypical depression: four definitions. Seishin Shinkeigaku Zasshi. 2010;112(1):3–22.
91. Akiskal HS. Delineating irritable and hyperthymic variants of the cyclothymic temperament. J Pers Disord. 1992;6(4):326–42.
92. Rihmer Z, Akiskal KK, Rihmer A, Akiskal HS. Current research on affective temperaments. Curr Opin Psychiatry. 2010;23(1):12–8.
93. Reich B, Zanarini M, Fitzmaurice G. Affective lability in bipolar disorder and borderline personality disorder. Compr Psychiatry. 2012;53:230–7.
94. Akiskal HS. Demystifying borderline personality: critique of the concept and unorthodox reflections on its natural kinship with the bipolar spectrum. Acta Psychiatr Scand. 2004; 110(6):403.
95. Levitt AJ, Joffe RT, Ennis J, MacDonald C, Kutcher SP. The prevalence of cyclothymia in borderline personality disorder. J Clin Psychiatry. 1990;51(8):335–9.
96. MacDonald K, Berlow R, Thomas ML. Attachment, affective temperament, and personality disorders: a study of their relationships in psychiatric outcomes. J Affect Disord. 2013;151(3): 932–41.
97. Stewart JW. Treating depression with atypical features. J Clin Psychiatry. 2007;68(S3): 25–9.
98. Beck AT, Rush AJ, Shaw BF, et al. Cognitive therapy of depression. Guilford clinical psychology and psychotherapy series. Guilford: New York; 1979.
99. Ingenhoven T, Lafay P, Rinne T, Passchier J, Duivenvoorden H. Effectiveness of pharmacotherapy for severe personality disorders: meta-analyses of randomized controlled trials. J Clin Psychiatry. 2010;71(1):14–25.
100. Ripoll LH, Triebwasser J, Siever LJ. Evidence-based pharmacotherapy for personality disorders. Int J Neuropsychopharmacol. 2011;14(9):1257–88.
101. Gunderson JG, Morey LC, Stout RL, Skodol AE, Shea MT, McGlashan TH, et al. Major depressive disorder and borderline personality disorder revisited: longitudinal interactions. J Clin Psychiatry. 2004;65(8):1049–56.

102. Parsons B, Quitkin FM, McGrath PJ, Stewart JW, Tricamo E, Ocepek-Welikson K, et al. Phenelzine, imipramine, and placebo in borderline patients meeting criteria for atypical depression. Psychopharmacol Bull. 1989;25(4):524–34.
103. Soloff PH, Cornelius J, George A, Nathan S, Perel JM, Ulrich RF. Efficacy of phenelzine and haloperidol in borderline personality disorder. Arch Gen Psychiatry. 1993;50(5):377–85.
104. Eisenberger NI, Way BM, Taylor SE, Welch VT, Lieberman MD. Understanding genetic risk for aggression: clues from the brain's response to social exclusion. Biol Psychiatry. 2007; 61(9):1100–8.
105. Neubauer H, Bermingham P. A depressive syndrome responsive to lithium: an analysis of 20 cases. J Nerv Ment Dis. 1976;163(4):276–81.
106. Akiskal HS, Khani MK, Scott-Strauss A. Cyclothymic temperamental disorders. Psychiatr Clin North Am. 1979;2(3):527–54.
107. Peselow E, Dunner D, Fieve R, Lautin A. Lithium prophylaxis of depression in unipolar, bipolar II, and cyclothymic patients. Am J Psychiatry. 1982;139(6):747–52.
108. Links PS, Steiner M, Boiago I, Irwin D. Lithium therapy for borderline patients: preliminary findings. J Pers Disord. 1990;4(2):173–81.
109. Van Meter AR, Youngstrom EA, Findling RL. Cyclothymic disorder: a critical review. Clin Psychol Rev. 2012;32(4):229–43.
110. Fava GA, Rafenelli C, Tomba E, Guidi J, Grandi S. The sequential combination of cognitive behavioral treatment and well-being therapy in cyclothymic disorder. Psychother Psychosom. 2011;80(3):136–43.
111. Lieb K, Völlm B, Rücker G, Timmer A, Stoffers JM. Pharmacotherapy for borderline personality disorder: Cochrane systematic review of randomised trials. Br J Psychiatry. 2010; 196(1):4–12.
112. Davidson K, Norrie J, Tyrer P, Gumley A, Tata P, Murray H, et al. The effectiveness of cognitive behavior therapy for borderline personality disorder: results from the borderline personality disorder study of cognitive therapy (BOSCOT) trial. J Pers Disord. 2006;20(5): 450–65.
113. Davidson KM, Tyrer P, Norrie J, Palmer SJ, Tyrer H. Cognitive therapy v. usual treatment for borderline personality disorder: prospective 6-year follow-up. The. Br J Psychiatry. 2010; 197(6):456–62.
114. Bateman A, Fonagy P. Psychotherapy for borderline personality disorder: mentalization based treatment (Bateman, psychotherapy for borderline personality disorder). Oxford/New York: Oxford University Press; 2004.
115. Clarkin JF, Yeomans F, Kernberg OF. Psychotherapy for borderline personality: focusing on object relations. New York: Wiley; 2006.
116. Bateman A, Fonagy P. 8-year follow-up of patients treated for borderline personality disorder: mentalization-based treatment as usual. Am J Psychiatry. 2008;165(5):631–8.
117. Linehan MM, Comtois KA, Murray AM, Brown MZ, Gallop RJ, Heard HL, et al. Two-year randomized controlled trial and follow-up of dialectical behavior therapy vs therapy by exports for suicidal behaviors and borderline personality disorder. Arch Gen Psychiatry. 2006;63(7):757–66.
118. McMain SF, Links PS, Gnam WH, Guimond T, Cardish RJ, Korman L, Streiner DL. A randomized trial of dialectical behavior therapy versus general psychiatric management for borderline personality disorder. Am J Psychiatry. 2009;166(12):1365–74.
119. McMain SF, Guimond T, Streiner DL, Cardish RJ, Links PS. Dialectical behavior therapy compared with general psychiatric management for borderline personality disorder: clinical outcomes and functioning over a 2-year follow-up. Am J Psychiatry. 2012;169(6):650–61.

Chapter 4
Is Borderline Personality Disorder Underdiagnosed and Bipolar Disorder Overdiagnosed?

Theresa A. Morgan and Mark Zimmerman

Introduction

Borderline personality disorder (BPD) is widely considered one of the most severe and chronic of the mental disorders [1, 2] and is associated with high public health costs [3], functional impairment, and clinical severity [4, 5]. Patients with BPD report heavy utilization of psychiatric services (including inpatient and partial hospitalizations, psychotherapy, and psychopharmacology management visits), criminal services due to violence or unlawful sexual behavior, nonpsychiatric medical services, and legal services such as divorce, libel, and child-related lawsuits [6].

BPD is diagnosed polythetically, and patients must meet threshold for 5 of 9 equally weighted diagnostic descriptors. These criteria include impulsivity, self-injurious behavior, stress-related psychosis, chronic emptiness, and instability with respect to interpersonal relationships, self-image, anger, and affect [7]. BPD is also the most commonly diagnosed personality disorder in clinical settings and is reported to occur in approximately 10 % of psychiatric outpatients and 15–20 % of psychiatric inpatients [1]. Community samples typically yield prevalence estimates around 1–2 % [1], though some studies report rates as high as 5–6 % [8]. Although the specific causes of BPD have yet to be identified, it is believed that a combination of multiple psychosocial and biological factors leads to maladaptive personality trait features characteristic of BPD [9].

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Is BPD Underdiagnosed?

The problem of underrecognition of personality pathology has been known for some time. Indeed, it was largely concern about underrecognition of personality disorders that originally led to the placement of these diagnoses on Axis II in DSM-III, to "ensure that consideration is given to the possible presence of disorders that are frequently overlooked when attention is directed to the usually more florid Axis I disorder" [10]. Despite the caution raised about underdiagnosing personality disorders, and their placement on Axis II, studies documented that clinicians use personality disorder diagnoses relatively infrequently [11, 12].

To be sure, due to the reliance on retrospective reporting and the ego-syntonic nature of personality disorders, diagnosing BPD in a clinical setting can be difficult. Westen noted that clinicians tend to rely on longitudinal perspectives to diagnose personality disorders, basing judgments on patients' descriptions, behavior, and attitudes during treatment sessions over time [11]. By extension, personality disorder diagnoses are rarely made during intake interviews, which tend to be time limited. Intake interviews tend to emphasize diagnosing Axis I disorders, which have a more immediate effect on treatment planning. Consequently, diagnostic rates tend to be much lower when BPD is diagnosed by clinicians using unstructured assessments than by interviewers using standardized interviews. For example, Oldham and Skodol examined the rate of DSM-III personality disorders in nearly 130,000 patients in the New York state hospital system [13]. Results showed that personality disorders were not being systematically diagnosed in this sample. Similar findings were reported in heterogeneous psychiatric samples from non-state hospitals [14].

Zimmerman and colleagues were the first group to directly compare BPD diagnostic rates using standard clinical interviewing, semi-structured clinical interviewing, and a combination condition where clinicians were presented with results from the semi-structured interview but did not conduct the interview themselves [12]. Rates of BPD were significantly higher in the structured interview group (14.4 %) than the clinical intake interview group (0.4 %). Frequency of BPD diagnoses also significantly increased when clinicians were provided the results from structured interviewing (9.2 %). Taken together, these findings suggest that even though they are not part of a regular intake interview, clinicians find value in and utilize diagnostic information provided by structured interviewing. Thus, the issue in diagnosing personality disorder appears to be more related to having sufficient time to conduct a thorough interview than to the need to rely on longitudinal observation.

Reasons for Underdiagnosis of BPD

There are many possible reasons for the underdiagnosis of BPD, one of which is lack of confidence in the construct. Personality disorder diagnoses are viewed by some as unreliable, lacking validity, and of secondary importance (see Clark [15] for a review). The structure of the BPD diagnosis has also resulted in much

disagreement among researchers and clinicians, with several authors proposing alternative, trait-based, or prototype-based approaches to the current categorical model [16, 17]. The polythetic criteria used to diagnose BPD also may lead to confusion. Because patients need only to meet 5 of 9 possible criteria, individuals who meet threshold for BPD may present very differently clinically which can be confusing. Indeed, there are 151 different ways to diagnose BPD using the "5 of 9" criteria met rule [1]. Even efforts to clarify the structure of BPD through factor modeling yield mixed results, with proposed models consisting of one to four factors [18]. These and other controversies regarding the validity of BPD can be confusing for clinicians and serve to dilute the perceived validity of the diagnosis.

BPD in particular has also been heavily criticized for high comorbidity rates with other disorders, which some authors suggest indicate the diagnosis is vague, improperly applied, or redundant [19, 20]. Others argue that the high comorbidity is better viewed as an index of clinical severity rather than being an indicator of low diagnostic independence [21, 22]. Thus, high comorbidity in BPD patients can be viewed as indicative of BPD's status as a heterogeneous disorder affecting multiple symptom dimensions. Practically, comorbidity in patients who have BPD may lead clinicians to overlook the disorder and only diagnose these comorbid disorders that are often the reason for seeking treatment. Indeed, although BPD is among the most commonly diagnosed of the Axis II disorders, clinicians frequently defer diagnosis on Axis II altogether.

Other possible reasons for underdiagnosis are more overtly clinical. Diagnosis with BPD is widely considered stigmatizing among mental healthcare providers [23], with one author describing the perception of BPD patients as "doomed to chronicity" [24]. Clinicians may thus be reluctant to give the diagnosis to reduce stigma for patients and potentially increase their likelihood of acceptance in the larger mental health system [25]. Many of the symptoms typical of BPD such as self-mutilating behavior, recurrent suicidal gestures and threats, and intense anger can be difficult for clinicians to manage. For these reasons the term "borderline personality disorder" is sometimes used in a pejorative, diminutive, or dismissive manner by clinicians to identify interpersonally difficult patients who may or may not actually meet criteria for BPD [26, 27]. Misuse of the term as an adjective rather than a proper noun may diminish the importance of assessing the BPD criteria in a clinical setting. Indeed, Morey and Ochoa showed that in a national sample of clinicians, personality disorder diagnoses were given without documentation of whether or not patients met specific diagnostic criteria [28].

Patients with BPD are also notoriously difficult to treat. Gunderson and colleagues reported that the typical BPD patient uses multiple service providers, switches therapists, and terminates treatment within the first 3 months [29]. BPD patients also account for approximately 15 % of psychiatric hospitalizations [30] and receive significantly more psychosocial treatments and more medication changes than do patients with other personality disorders or major depression [3]. For these reasons, clinicians may wish to spare patients from diagnosing a disorder with this unfavorable prognosis in ambiguous cases.

Underdiagnosis of BPD may also be linked to the disorder's phenomenological overlap and high comorbidity with impulse control disorders, mood disorders, anxiety disorders, and substance and alcohol use disorders, among others. In particular, BPD has been commonly studied with respect to bipolar disorders, and some researchers consider the disorders to exist along the same spectrum [31].

Overdiagnosis of Bipolar Disorder and BPD

Like BPD, bipolar disorder is also associated with clinical severity, chronicity, high public health costs, and functional impairment [32]. Much has been written about the underdiagnosis of bipolar disorder, and the underrecognition of bipolar disorder has been identified as a significant clinical problem [33–35]. Indeed, for patients who are ultimately diagnosed with bipolar disorder, the time between initial treatment seeking and the diagnosis of bipolar disorder is frequently more than 10 years [36, 37]. These and other researchers also suggest that the misdiagnosis of bipolar disorder as unipolar depression is particularly concerning, primarily due to the subsequent ineffective overuse of antidepressants and underuse of mood stabilizers [38].

More recently, there have also been some reports of overdiagnosis of bipolar disorder. For example, Hirschfeld and colleagues administered the SCID to 180 outpatients on antidepressant medication [39]. Of this sample, 43 patients (23.8 %) reported a prior diagnosis of bipolar disorder, of whom 32.6 % did not have the diagnosis confirmed by the SCID. In contrast, only 21.9 % of patients reporting no history of bipolar disorder were diagnosed with bipolar disorder on the SCID. Stewart and El-Mallakh evaluated 21 patients in residential treatment for substance use who reported a previous diagnosis with bipolar disorder [40]. After SCID interviewing, only 9 (43 %) of these patients were diagnosed with bipolar disorder. Goldberg and colleagues evaluated 85 patients admitted to a dual-diagnosis inpatient unit who had previously been diagnosed with bipolar disorder by an outpatient psychiatrist [41]. Similar to Stewart and El-Mallakh, only 28 patients (33 %) had the diagnosis of bipolar disorder confirmed.

In the process of conducting clinical assessments, one group observed an increasing number of patients reporting a history of being diagnosed with bipolar disorder [42]. The authors subsequently assessed a large sample of psychiatric outpatients using semi-structured diagnostic interviewing for DSM-IV Axis I disorders, 20.7 % of whom reported a previous diagnosis with bipolar disorder. Less than half of these patients (43.4 %) ultimately met criteria for bipolar disorder, an overdiagnosis rate of more than 50 %. The authors validated their diagnostic methodology by finding a significantly higher morbid risk of bipolar disorder in the first-degree relatives of patients diagnosed with bipolar disorder compared to patients who were overdiagnosed with bipolar disorder.

The same authors speculated that bipolar overdiagnosis would be most common in patients diagnosed with borderline personality disorder. A subsequent report

from their study confirmed this hypothesis, showing that approximately 25 % of patients who had been overdiagnosed with bipolar disorder were diagnosed with BPD. Similarly, nearly 40 % of the patients ultimately diagnosed with BPD reported a history of overdiagnosis with bipolar disorder [43].

In a third report from this group, Ruggero and colleagues examined whether specific symptoms of BPD increased the odds of bipolar disorder misdiagnosis [44]. The authors compared two groups: 82 patients reporting previous diagnosis of bipolar disorder but who did not have bipolar disorder after SCID interviewing and 528 patients who had never been diagnosed with bipolar disorder. With the exception of transient dissociation, all BPD criteria were associated with increased odds of a previous misdiagnosis with bipolar disorder. Interestingly, patients endorsing more than six BPD criteria were less likely to have a history of misdiagnosis, raising the intriguing possibility that the diagnosis became more clear as the number of criteria met increased.

Somewhat similar results were reported by Meyerson [45]. Here, 70 patients were identified as having BPD using clinical research methodology for DSM-IV. Nearly three quarters of these patients denied a history of diagnosis with BPD, and the majority of these reported being given one or more additional Axis I diagnoses. The most common "false-positive" diagnoses were mood disorders, particularly bipolar disorder (17 %) and major depressive disorder (13 %). These results are particularly surprising given that the patients also reported an average of 10.4 years since their first psychiatric encounter and presumably had multiple contacts with treatment professionals during this time. These data replicated those documenting overdiagnosis of bipolar disorder in patients with BPD [42].

Reasons for Misdiagnosis

Emerging research clearly suggests a pattern of overdiagnosis of bipolar disorder in patients with BPD. Reasons for this pattern vary, but the primary cause appears to be phenomenological similarities between the disorders. For example, both BPD and bipolar disorder are characterized by mood fluctuations. However, the intense emotionality that occurs in patients with BPD is typically time-limited and reactive to external influences, such as interpersonal cues. In bipolar disorder, mood dysregulation is sustained (at least 1 week for mania and 4 days for hypomania) and less contingent on the environment. Patients with BPD also commonly experience shifts from euthymia to anger or anxiety, whereas in bipolar disorder, the shift is more commonly described as euthymia to elation or depression (or from elation directly to depression [46]). Similarly, patients with BPD frequently report potentially harmful impulsivity, including in the areas of gambling, excessive spending, sexual promiscuity, theft, eating binges, reckless driving, and excessive alcohol and substance use. Patients with bipolar disorder will also report these behaviors. However, in bipolar patients potentially dangerous impulsivity is typically limited to episodes of mania or hypomania, whereas in patients with BPD, impulsivity is

trait-like and thus consistent across mood states [47]. Other shared clinical features include high rates of depression, comorbidity (particularly anxiety and substance use disorders), early age of onset, and suicidality. Insufficient diagnostic rigor—due to inattention, lack of time, or lack of available resources to conduct a thorough interview—may lead to misdiagnosis based on these shared characteristics.

A related issue is familiarity with diagnosis and treatment of a disorder. Diagnosing BPD accurately requires experience with the phenomenology of the disorder, as well as ready knowledge of the nine diagnostic criteria associated with BPD. Providers may be more comfortable treating bipolar disorder than BPD, which could affect their tendency to overdiagnose bipolar disorder in patients with ambiguous symptoms. Prescribing clinicians in particular may err on the side of diagnosing a disorder that is responsive to medication (bipolar) versus diagnosing BPD, which is typically treated psychotherapeutically. Moreover, BPD is notoriously difficult to treat, and patients report frequent changes to treatment providers, inpatient and partial hospitalizations, and suicide attempts [48]. Probably due to the difficulties in treating such patients, BPD is also widely stigmatized among treatment professionals [23]. Although bipolar patients also report high clinical severity and impairment, they generally lack the interpersonal difficulties inherent in treating patients with BPD, resulting in comparatively less stigma associated with bipolar disorder. For these reasons, providers may be reluctant to deliver a diagnosis of BPD to their patients when presenting symptoms are ambiguous. Patients themselves may also be motivated to retain a diagnosis of bipolar disorder once it is delivered, possibly due to secondary gain such as disability payments [49].

Also relevant is the increasing availability of medications to treat bipolar disorder, as well as marketing efforts to promote these medications that are aimed at both clinicians and patients. Direct-to-consumer advertising in particular may lead consumers to screening questionnaires that, although helpful, tend to maximize sensitivity (thus increasing false-positives) in the presumption of follow-up with a clinical evaluation. As noted in Zimmerman et al. [42], many continuing medical education programs on bipolar disorder include a summary of research on underrecognition of bipolar disorder. There is no such ground force promoting BPD engineered by pharmaceutical companies, and presentations are rarely balanced by a concordant discussion of research showing that bipolar disorder is overdiagnosed or detailing the risks of overdiagnosis. As such, medical doctors may not receive a balanced education with respect to diagnostic patterns and consequently may err on the side of overdiagnosis without giving full consideration to the risks of this bias. Of course diagnostic confusion could result in overdiagnosis of either bipolar disorder or BPD. However, we would hypothesize a bias towards more bipolar disorder overdiagnosis due to the reasons detailed in this section, specifically clinicians' greater familiarity with the diagnosis and treatment of bipolar disorder, the stigma associated to the BPD diagnosis due to interpersonal conflict, and the greater promotion and availability of medications for the treatment of bipolar disorder.

Should BPD Be Considered to Be Part of the Bipolar Spectrum?

The sharing of features and high comorbidity of BPD and bipolar disorder have led some to suggest that BPD is on the "bipolar spectrum." These researchers suggest that the DSM-IV criteria for bipolar disorder are overly narrow and should be expanded to include milder forms of the disorder, which would include BPD [31, 50, 51]. For example, several studies criticize the DSM-IV duration criteria for manic and hypomanic episodes as being too long, suggesting that individuals with hypomanic episodes lasting 2 days should also be included in the bipolar disorder diagnosis [52]. Broadening the diagnosis to include subthreshold cases would decrease the rate of overdiagnosis simply by increasing diagnostic rates overall, particularly in the case of depressed patients with comorbid borderline personality disorder who also report intense affective experiences that may be reinterpreted as bipolar disorder [53]. However, several recent reviews of the BPD and bipolar disorder literature do not support the inclusion of BPD as a bipolar spectrum disorder [54, 55], and the disorders remain distinct in the recent revision to the diagnostic and statistical manual [7].

Multiple review articles have summarized the evidence in support of and in opposition to the hypothesis that BPD belongs in the bipolar spectrum [25, 54, 55]. These reviews report that relatively few studies have directly compared individuals diagnosed with BPD and bipolar disorder. Importantly, those studies that do provide this comparison are generally based on small samples and examine a limited number of variables. For example, Atre-Vaidya and Hussain compared personality traits in 10 patients with BPD to 13 patients with bipolar disorder [56]. Results showed differences on 3 of 7 dimensions of the Temperament and Character Inventory. Similarly, Berrocal and colleagues [57] compared 25 BPD patients without a history of mood disorders, 16 patients with bipolar disorder without a history of BPD, and 19 patients with comorbid MDD and BPD on a self-report measure of mood phenomenology. Results showed no significant differences between BPD and bipolar disorder. A comparison of female outpatients with bipolar I disorder ($n=25$) and BPD ($n=31$) showed significantly higher cyclothymic, depressive, irritable, and anxious temperament in BPD patients [58]. BPD patients also scored higher on 14 of 18 measured indices of maladaptive self-schemas in this study. A final study comparing BPD ($n=10$) and bipolar II disorder ($n=9$) showed differences in types of psychodynamic conflicts reported, but not on defense mechanisms used [59].

Henry and colleagues compared four groups: 29 patients with BPD (no bipolar disorder), 14 patients with bipolar II disorder (no BPD), 12 patients with BPD and bipolar II disorder, and a control group of 93 patients with another PD (but no bipolar disorder or BPD) [46]. Results showed that both BPD and bipolar disorder were characterized by affective lability and that lability in BPD groups was associated with greater impulsivity and hostility as compared to patients without BPD.

Another study also compared four slightly different groups: 72 patients with comorbid BPD and MDD, 15 depressed patients with bipolar II (no BPD), 15 depressed patients with comorbid bipolar II and BPD, and a control group of 71 MDD patients (no BPD) [60]. As was previously reported [46], patients with BPD reported significantly higher levels of impulsiveness and hostility, as well as cognitive and anxious symptoms. However, both these studies report two-way analyses of variance with the presence/absence of BPD and bipolar II as the primary factors. Thus, the significant differences may be due to differences with patients without either BPD or bipolar [46] or to differences with the MDD only group [60].

Finally, Zimmerman and colleagues compared 62 patients with bipolar II depression (no BPD) and 206 with comorbid MDD and BPD (no bipolar disorder) on a wide number of clinical and family history variables [61]. Results showed that the MDD-BPD patients were significantly more likely to be diagnosed with posttraumatic stress disorder, a current substance use disorder, somatoform disorder, and other (non-BPD) personality disorders. The MDD-BPD group also reported significantly higher ratings of recent anger, anxiety, paranoid ideation, and somatization. The MDD-BPD group also was rated lower on several functioning variables (particularly social functioning) and reported a higher number of suicide attempts. In contrast, patients with bipolar II depression had a significantly higher morbid risk for bipolar disorder in first-degree relatives than did MDD-BPD patients.

Although the majority of these studies are limited by a small sample size and small number of variables studied, the studies are consistent in finding symptom and personality trait differences that distinguish BPD from bipolar disorder. Thus, these findings provide support for the continued conceptualization of BPD and bipolar disorder as valid and distinct diagnoses.

It is important to note that changing the diagnostic threshold for bipolar disorder would have a significant effect on the prevalence of this diagnosis, as well as that of diagnoses that share features of bipolar disorder (such as BPD). Zimmerman provides an in-depth discussion of this issue, including the important point that while broadening the bipolar spectrum would decrease the rate of false-negatives (underdiagnosis), it would also result in an increased rate of false-positives (overdiagnosis) [62].

Thus, although it is clear that bipolar disorder is commonly misdiagnosed in cases involving BPD, it is also possible that bipolar disorder is underdiagnosed in certain situations. Indeed, underdiagnosis of bipolar disorder was a consensus among researchers for many years [31, 37, 38, 63]. However, more recent reports show a shift in this trend, with rate of bipolar diagnosis doubling in adults and becoming nearly 40 times more common in children and adolescents [64]. We believe the sudden rise in bipolar diagnosis combined with findings from our lab and others showing the misdiagnosis of bipolar disorder in certain cases more strongly suggests a trend towards overdiagnosis.

Treatment Implications

The question of whether a patient has bipolar disorder, BPD, or comorbid bipolar and BPD has important implications for treatment. The efficacy of pharmacological treatments for bipolar disorder is well established [65]. In contrast, no medications have been approved for the treatment of BPD, although some medications show efficacy for aspects of the disorder [66]. Also relevant is the robust finding that medication for depression is less effective in patients with comorbid personality disorder [67]. Moreover, only mixed evidence suggests that medications used to treat bipolar disorder are effective treatments for BPD. In a review of this literature, Binks and colleagues concluded that randomized control trials of pharmacological treatment for BPD in general do not provide clear evidence for medication use in BPD patients [68].

In contrast, a preponderance of evidence also shows that patients with BPD benefit most from focused therapeutic interventions such as Dialectical Behavior Therapy [69, 70], Cognitive Behavioral Therapy [71, 72], Schema-Focused Therapy [73], adjunctive group psycho-education with systems based therapy [74, 75], and Mentalization-Based and Transference-Focused Therapies [76, 77]. Because these therapies were designed for features unique to BPD, their effectiveness at improving symptoms of bipolar disorder is unknown. Diagnosing bipolar disorder in patients who actually have BPD could result in failure to recommend the most appropriate treatment, which at best could minimally effect symptoms and impairment and at worst could result in the patient and/or the clinician becoming disillusioned, disengaged, or frustrated with treatment generally. One study documented that among patients diagnosed with BPD, prior misdiagnoses were significantly associated with higher medication rates [45]. The unnecessary prescription of mood stabilizers—the treatment of choice for bipolar disorder—could expose patients to serious medication side effects [42].

Given the superficial overlap in phenomenology, it is important to identify additional clinical markers to differentiate bipolar disorder and BPD. One such clinical indicator is the presence or absence of a family history of bipolar disorder. Family history may be used to identify BPD, and one study reported 63 % heritability for BPD [78]. However, family history data often relies on the accurate retrospective reporting by the patient, and a small number of outpatients with BPD also report a family history of bipolar disorder (3 % per one article [79]). Another indicator that is commonly used to identify BPD is the presence of childhood trauma, which is reported in 30–90 % of BPD patients [80]. However, a high number of bipolar disorder patients also describe some form of abuse or neglect in childhood [81]. Similarly, although BPD is frequently characterized by interpersonal problems, a high number of interpersonal difficulties are also reported by bipolar patients [82]. Thus, although indicators such as family history and childhood trauma can point in a particular direction, they are not, in themselves, diagnostic. Paris suggested that differential diagnosis of BPD and other disorders will ultimately come to rely on clinical indictors such as biological testing, imaging, and genetic information [21]; however, these markers have yet to be identified.

Conclusions

Recent reports suggest that bipolar disorder is often misdiagnosed or overdiagnosed. A pattern to this misdiagnosis has also emerged, showing that bipolar disorder is particularly likely to be misdiagnosed in patients who after careful diagnostic interviewing ultimately meet criteria for BPD (among other disorders). The pattern of misdiagnosis in no way diminishes the import of the bipolar diagnosis. Rather, we believe these findings further serve to underscore the need for careful, clinical assessment at intake across settings. Indeed, it would appear that psychiatric care providers agree as, even when they do not conduct semi-structured interviews themselves, clinicians trust the information from these interviews [83].

Taken together, our findings underscore some of the difficulties inherent not only to diagnosis of BPD and bipolar disorder specifically but of psychiatric phenomena generally. At present, the vast majority of psychiatric disorders are diagnosed based on clinical phenomenology and patient self-report. These sources of information are frequently inconsistent, unclear, or limited in scope, which renders diagnostic decisions even more difficult, particularly under time pressure. Nonetheless, chronic underdiagnosis of BPD has significant, real-world consequences in terms of treatment planning and implementation. The same implications apply for bipolar disorder. As such, it will be important for future clinical researchers to better delineate these disorders conceptually and for this information to be disseminated into clinical practice as seamlessly as possible.

References

1. Skodol AE, Gunderson JG, Pfohl B, Widiger TA, Livesley JW, Siever LJ. The borderline diagnosis I: psychopathology, comorbidity, and personality structure. Biol Psychiatry. 2002;51: 936–50.
2. Skodol AE, Pagano ME, Bender DS, Shea MT, Gunderson JG, Yen S, et al. Stability of functional impairment in patients with schizotypal, borderline, avoidant, or obsessive-compulsive personality disorder over two years. Psychol Med. 2004;35:443–51.
3. Bender DS, Dolan RT, Skodol AE, Sanislow CA, Dyck IR, McGlashan TH, et al. Treatment utilization by patients with personality disorders. Am J Psychiatry. 2001;158:295–302.
4. Nakao K, Gunderson JG, Phillips KA, Tanaka N, Yorifuji K, Takaishi J, et al. Functional impairment in personality disorders. J Pers Disord. 1992;6:24–33.
5. Zimmerman M, Chelminski I, Young D, Martinez J, Morgan TA. Which DSM-IV personality disorders are most strongly linked with indices of psychosocial morbidity in psychiatric outpatients? Compr Psychiatry. 2012;53:940–5.
6. Gunderson JG. Borderline personality disorder: ontogeny of a diagnosis. Am J Psychiatry. 2009;166:530–9.
7. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013.
8. Grant BF, Chou SP, Goldstein RB, Huang B, Stinson FS, Saha TD, et al. Prevalence, correlates, disability, and comorbidity of DSM-IV borderline personality disorder: results from the Wave2 National Epidemiologic Survey on Alcohol and Related Conditions. Psychiatry. 2008; 69:533–45.

9. Livesly J. Toward a genetically-informed model of borderline personality disorder. J Pers Disord. 2008;22:42–71.
10. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 3rd ed. Washington, DC: American Psychiatric Association; 1987.
11. Westen D. Divergences between clinical and research methods for assessing personality disorders: implications for research and the evolution of axis II. Am J Psychiatry. 1997;154: 895–903.
12. Zimmerman M, Mattia J. Differences between clinical and research practices in diagnosing borderline personality disorder. Am J Psychiatry. 1999;156:1570–4.
13. Oldham JM, Skodol AE. Personality disorders in the public sector. Hosp Community Psychiatry. 1991;42:481–7.
14. Koenigsberg HW, Kaplan RD, Gilmore MM, Cooper AM. The relationship between syndrome and personality disorder in DSM-III: experience with 2,462 patients. Am J Psychiatry. 1985; 142:207–12.
15. Clark LA. Assessment and diagnosis of personality disorder: perennial issues and an emerging reconceptualization. Annu Rev Psychol. 2007;58:227–57.
16. Krueger RF, Eaton NR, Clark LA, Watson D, Markon KE, Derringer J, et al. Deriving an empirical structure of personality pathology for DSM-5. J Pers Disord. 2001;25:170–91.
17. Westen D, DeFife JA, Bradley B, Hilsenroth MJ. Prototype personality diagnosis in clinical practice: a viable alternative for DSM-5 and ICD-11. Prof Psychol Res Pr. 2010;41:482–7.
18. Chmielewski M, Bagby RW, Quilty LC, Paxton R, McGee Ng SA. A (re-)-evaluation of the symptom structure of borderline personality disorder. Can J Psychiatry. 2001;56:530–9.
19. Nurnberg HG. The comorbidity of borderline personality disorder and other DSM-III-R axis II personality disorders. Am J Psychiatry. 1991;148:1371–7.
20. Tyrer P. Borderline personality disorder: a motley diagnosis in need of reform. Lancet. 1999;354:18–25.
21. Paris J. The diagnosis of borderline personality disorder: problematic but better than the alternatives. Ann Clin Psychiatry. 2005;17:41–6.
22. Zanarini MC, Frankenburg FR, Khera GS, Bleichmar J. Treatment histories of borderline inpatients. Compr Psychiatry. 2001;42:144–50.
23. Aviram RB, Brodsky BS, Stanley B. Borderline personality disorder, stigma, and treatment implications. Harv Rev Psychiatry. 2006;14:249–56.
24. Paris J. The outcome of borderline personality disorder: good for most but not all patients. Am J Psychiatry. 2012;169:445–6.
25. Paris J, Gunderson J, Weinberg I. The interface between borderline personality disorder and bipolar spectrum disorders. Compr Psychiatry. 2007;48:145–54.
26. Lewis G, Appleby L. Personality disorder: the patients psychiatrists dislike. Br J Psychiatry. 1988;153:44–9.
27. Reiser DE, Levenson H. Abuses of the borderline diagnosis: a clinical problem with teaching opportunities. Am J Psychiatry. 1984;141:1528–32.
28. Morey LC, Ochoa ES. An investigation of adherence to diagnostic criteria: clinical diagnosis of the DSM-III personality disorders. J Pers Disord. 1989;3:180–92.
29. Gunderson JG, Frank AF, Ronningstam EF, Wachter S, Lynch VJ, Lynch PJ. Early discontinuance of borderline patients from psychotherapy. J Nerv Ment Dis. 1989;177:38–42.
30. Widiger TA, Weissman MM. Epidemiology of borderline personality disorder. Hosp Community Psychiatry. 1991;42:1015–21.
31. Akiskal HS, Bourgeois ML, Angst J, Post R, Moller H, Hirschfeld R. Re-evaluating the prevalence of and diagnostic composition within the broad clinical spectrum of bipolar disorders. J Affect Disord. 2000;59:S5–30.
32. Zarata CA, Tohen M, Land M, Cavanagh S. Functional impairment and cognition in bipolar disorder. Psychiatr Q. 2000;71:309–29.
33. Bowden CL. Strategies to reduce misdiagnosis of bipolar depression. Psychiatr Serv. 2001; 52:51–5.

34. Ghaemi S. Insight and psychiatric disorder: a review of the literature, with a focus on its clinical relevance for bipolar disorder. Psychiatr Ann. 1997;27:782–90.
35. Hirschfeld RM. Bipolar spectrum disorder: improving its recognition and diagnosis. J Clin Psychiatry. 2001;62:5–9.
36. Hirschfeld RM, Lewis L, Vornik LA. Perceptions and impact of bipolar disorder: how far have we really come? Results of the national depressive and manic-depressive association 2000 survey of individuals with bipolar disorder. J Clin Psychiatry. 2003;64:161–74.
37. Lish JD, Dime-Meenan S, Whybrow PC, Price RA, Hirschfeld RM. The national depressive and manic-depressive association (DMDA) survey of bipolar members. J Affect Disord. 1994;31:281–94.
38. Ghaemi SN, Sachs GS, Chiou AM, Pandurangi AK, Goodwin K. Is bipolar disorder still underdiagnosed? Are antidepressants overutilized? J Affect Disord. 1999;52:135–44.
39. Hirschfeld RM, Cass AR, Holt DC, Carlson CA. Screening for bipolar disorder in patients treated for depression in a family medicine clinic. J Am Board Fam Pract. 2005;18:233–9.
40. Stewart C, El-Mallakh RS. Is bipolar disorder overdiagnosed among patients with substance abuse? Bipolar Disord. 2007;9:646–8.
41. Goldberg J, Garno J, Callahn A, Kearns D, Kerner B, Ackerman S. Overdiagnosis of bipolar disorder among substance use disorder inpatients with mood instability. J Clin Psychiatry. 2008;69:1–7.
42. Zimmerman M, Ruggero CJ, Chelminski I, Young D. Is bipolar disorder overdiagnosed? J Clin Psychiatry. 2008;69:935–40.
43. Zimmerman M, Ruggero CJ, Chelminski I, Young D. Psychiatric diagnoses in patients previously overdiagnosed with bipolar disorder. J Clin Psychiatry. 2010;71:26–31.
44. Ruggero CJ, Zimmerman M, Chelminski I, Young D. Borderline personality disorder and the misdiagnosis of bipolar disorder. J Psychiatr Res. 2010;44:405–8.
45. Meyerson D. Is borderline personality disorder under diagnosed?. Paper presented at the annual conference of the American Psychiatric Association. 2009;Abstract SCR18-051.
46. Henry C, M'Bailara K, Desage A, Gard S, Misdrahi D, Vieta E. Towards a reconceptualization of mixed states, based on an emotional reactivity dimensional model. J Affect Disord. 2007; 101:35–41.
47. Dowson J, Bazanis E, Rogers R, Prevost A, Taylore P, Meux C, et al. Impulsivity in patients with borderline personality disorder. Compr Psychiatry. 2004;45:29–36.
48. Lieb K, Zanarini MC, Schmahl C, Linehan MM, Bohus M. Borderline personality disorder. Lancet. 2004;364:453–61.
49. Zimmerman M, Galione JN, Ruggero CJ, Chelminski I, Dalrymple K, Young D. Overdiagnosis of bipolar disorder and disability payments. J Nerv Ment Dis. 2010;198:452–4.
50. Angst J, Cassano G. The mood spectrum: improving the diagnosis of bipolar disorder. Bipolar Disord. 2005;7 suppl 4:4–12.
51. Ghaemi SN, Ko JY, Goodwin FK. "Cade's disease" and beyond: misdiagnosis, antidepressant use, and a proposed definition for bipolar spectrum disorder. Can J Psychiatry. 2002;47: 125–34.
52. Benazzi F. Is 4 days the minimum duration of hypomania in bipolar II disorder? Eur Arch Psychiatry Clin Neurosci. 2001;251:32–4.
53. Zimmerman M, Ruggero CJ, Chelminski I, Young D. Clinical characteristics of depressed outpatients previously overdiagnosed with bipolar disorder. Compr Psychiatry. 2008;51: 99–105.
54. Paris J. Borderline or bipolar? Distinguishing borderline personality disorder from bipolar spectrum disorders. Harv Rev Psychiatry. 2004;12:140–5.
55. Smith DJ, Muir WJ, Blackwood DH. Is borderline personality disorder part of the bipolar spectrum? Harv Rev Psychiatry. 2004;12:133–9.
56. Atre-Vaidya N, Hussain SM. Borderline personality disorder and bipolar mood disorder: two distinct disorders or a continuum? J Nerv Ment Dis. 1999;187:313–5.
57. Berrocal C, Ruiz Moreno MA, Rando MA, Benvenuti A, Cassano GB. Borderline personality disorder and mood spectrum. Psychiatry Res. 2008;159:300–7.

58. Nilsson AK, Jorgensen CR, Straarup KN, Licht RW. Severity of affective temperament and maladaptive self-schemas differentiate borderline patients, bipolar patients, and controls. Compr Psychiatry. 2010;51:486–91.
59. Perry JC, Cooper SH. A preliminary report on defenses and conflicts associated with borderline personality disorder. J Am Psychoanal Assoc. 1986;34:863–93.
60. Wilson ST, Stanley B, Oquendo MA, Goldberg P, Zalsman G, Mann JJ. Comparing impulsiveness, hostility, and depression in borderline personality disorder and bipolar II disorder. J Clin Psychiatry. 2007;68:1533–9.
61. Zimmerman M, Martinez JH, Morgan TA, Young D, Chelminski I, Dalrymple K. Distinguishing bipolar II depression from major depressive disorder with comorbid borderline personality disorder: demographic, clinical and family history differences. J Clin Psychiatry. 2013;74: 880–6.
62. Zimmerman M. Would broadening the diagnostic criteria for bipolar disorder do more harm than good? Implications from longitudinal studies of subthreshold conditions. J Clin Psychiatry. 2012;73:437–44.
63. Hirschfeld RM, Vornick LA. Recognition and diagnosis of bipolar disorder. J Clin Psychiatry. 2004;65:5–9.
64. Moreno C, Laje G, Blanco C, Jiang H, Schmidt AB, Olfson M. National trends in the outpatient diagnosis and treatment of bipolar disorder in youth. Arch Gen Psychiatry. 2007;64: 1032–9.
65. Gershon S, Chengappa KNR, Malhi GS. Lithium specificity in bipolar illness: a classic agent for the classic disorder. Bipolar Disord. 2009;11:34–44.
66. Soloff PH. Psychopharmacology of borderline personality disorder. Psychiatr Clin North Am. 2000;23:169–92.
67. Shea MT, Pilkonis PA, Beckham E, Collins JF, Elikin E, Sotsky SM, Docherty JP. Personality disorders and treatment outcome in the NIMH Treatment of Depression Collaborative Research Program. Am J Psychiatry. 1990;147:711–8.
68. Binks CA, Fenton M, McCarthy L, Lee T, Adams CE, Duggan C. Pharmacological interventions for people with borderline personality disorder. Cochrane Database Syst Rev. 2006; (1):CD005653.
69. Linehan MM, Comtois KA, Murray AM, Brown MZ, Gallop RJ, Heard HL, et al. Two-year randomized controlled trial and follow-up of dialectical behavior therapy vs. therapy by experts for suicidal behaviors and borderline personality disorder. Arch Gen Psychiatry. 2006;63:757–66.
70. Stanley B, Brodsky B, Nelson JD, Dulit R. Brief dialectical behavior therapy (DBT-B) for suicidal behavior and non-suicidal self-injury. Arch Suicide Res. 2007;11:337–41.
71. Davidson K, Norrie J, Tyrer P, Gumley A, Tata P, Murray H, et al. The effectiveness of cognitive behavior therapy for borderline personality disorder: results from the borderline personality disorder study of cognitive therapy (BOSCOT) trial. J Pers Disord. 2006;20:450–65.
72. Weinberg I, Gunderson JG, Hennen J, Cutter CJ. Manual assisted cognitive treatment for deliberate self-harm in borderline personality disorder patients. J Pers Disord. 2006;20: 482–92.
73. Giesen-Bloo J, van Dyck R, Spinhoven P, van Tilburg W, Dirksen C, van Asselt T, et al. Outpatient therapy for borderline personality disorder: randomized trial of schema-focused therapy vs, transference-focused psychotherapy. Arch Gen Psychiatry. 2006;63:649–58.
74. Blum N, Pfohl B, John DS, Monahan P, Black DW. STEPPS: a cognitive-behavioral systems-based group treatment for outpatients with borderline personality disorder—a preliminary report. Compr Psychiatry. 2002;43:301–10.
75. Blum N, St John D, Pfohl B, Stuart S, McCormick B, Allen J, et al. Systems training for emotional predictability and problem solving (STEPPS) for outpatients with borderline personality disorder: a randomized controlled trial and 1-year follow-up. Am J Psychiatry. 2008;165: 468–78.
76. Bateman A, Fonagy P. 8-year follow-up of patients treated for borderline personality disorder: mentalization-based treatment versus treatment as usual. Am J Psychiatry. 2008;165:631–8.

77. Clarkin JF, Levy KN, Lenzenweger MF, Kernberg OF. Evaluating three treatments for borderline personality disorder. Am J Psychiatry. 2007;164:922–8.
78. Torgersen S, Lygren S, Øien PA, Skre I, Onstad S, Edvardsen J, et al. A twin study of personality disorders. Compr Psychiatry. 2000;41:416–25.
79. Zimmerman M, Martinez J, Young D, Chelminski I, Dalrymple K. Differences between patients with borderline personality disorder who do and do not have a family history of bipolar disorder. Compr Psychiatry. 2014; Article in press.
80. Zanarinia MC, Williams AA, Lewis RE, Reich RB, Vera SC, Marino MF, et al. Reported pathological childhood experiences associated with the development of borderline personality disorder. Am J Psychiatry. 1997;154:1101–6.
81. Etain B, Mathieu F, Henry C, Raust A, Roy I, Germain A, et al. Preferential association between childhood emotional abuse and bipolar disorder. J Trauma Stress. 2010;23:376–83.
82. Perugi G, Toni C, Travierso MC, Akiskal HS. The role of cyclothymia in atypical depression: toward a data-based reconceptualization of the borderline-bipolar connection. J Affect Disord. 2003;73:87–98.
83. Zimmerman M, Mattia J. Psychiatric diagnosis in clinical practice: is comorbidity being missed? Compr Psychiatry. 1999;40:182–91.

Chapter 5
Affective Instability: Bipolar Disorder Versus Borderline Personality Disorder

D. Bradford Reich

Introduction

Affective instability is an important feature of both borderline personality disorder (BPD) and bipolar disorder. The DSM-V includes affective instability in its descriptions of BPD and bipolar disorder [1]. Research in BPD has suggested that affective instability is a core symptom of this disorder [2]. Research on bipolar disorder has suggested that bipolar patients have significant affective instability during both symptomatic and euthymic periods [3, 4]. There is significant debate about the overlap between BPD and bipolar disorder [5, 6]. Thus, understanding the individual characteristics of affective instability in BPD and bipolar disorder may improve our understanding of the relationship between these disorders (Table 5.1).

The Concept of Affective Instability

Researchers have proposed that affective instability is comprised of multiple dimensions. These generally include: (1) frequency of affective changes; (2) amplitude of affective changes, particularly shifts from positive into negative affective states; (3) quality of affective changes; (4) temporal dependence, i.e., trends in affective instability related to factors such as time and overall mood intensity; (5) overall negative mood intensity; (6) mood reactivity in response to environmental triggers; and (7) difficulties with affective regulation [7–10]. This chapter will deal primarily with components 1–3 and 6–7.

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Table 5.1 Differences in affective instability

	BPD	Bipolar II
Differences in affective instability	↑ Freq and ↑ intensity shifts: Euthymia ↔ anger Depression ↔ anxiety	↑ Freq and ↑ intensity shifts Euthymia ↔ elation Depression ↔ elation
		↑ Positive emotion subscale scores

Renaud has proposed that affective instability be distinguished from mood lability and that affective lability be considered a subconstruct of affective instability [7]. She notes that affects are generally short-lived reactions to stimuli that last only minutes. Moods, in contrast, refer to more sustained affective states. She proposes that mood lability applies to the cycling of affective states that occurs in bipolar disorder. She suggests that affective lability is a temperamental vulnerability toward strong and rapid affective shifts in response to environmental stimuli that would produce less extreme affective changes in normal individuals. She proposes that mood instability, while not defined in the literature, generally refers to fluctuations within an abnormal mood state. She concludes that affective lability is a more accurate term than mood lability because there is no reported association between number of major mood episodes and self-reported mood lability.

The DSM-V discusses affective or mood instability in relation to both BPD and bipolar disorder. It defines affective instability in BPD as follows:

> Individuals with Borderline Personality Disorder may display affective instability that is due to a marked reactivity of mood (e.g., intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and only rarely last more than a few days). The basic dysphoric mood of those with Borderline Personality Disorder is often disrupted by periods of anger, panic, or despair and is rarely relieved by periods of well-being or satisfaction. These episodes may reflect the individual's extreme reactivity to interpersonal stresses [1].

In its discussion of manic states in bipolar I disorder, the DSM-V states: "Rapid shifts in mood may occur over brief periods of time and are referred to as lability (i.e., the alternation between euphoria, dysphoria, and irritability)" [1]. In its discussion of mixed manic states, it states:

> Mood may shift very rapidly to anger or depression. Depressive symptoms may occur during a manic episode and, if present, may last moments, hours, or, more rarely, days [1].

These descriptions of affective or mood shifts involve emotions that can be interpreted as overlapping. While the descriptions of a manic episode, a depressive episode, and BPD all include irritability, the description of BPD affective instability also refers to the related emotion anger. The description of affective instability in BPD mentions despair in comparison with the description of a mixed state in bipolar, which includes depression. The description of mood instability in bipolar disorder includes anxiety and panic. The DSM-V describes one type of mania that includes anxious distress [1]. The two descriptions of affective or mood instability differ most clearly in one respect. Whereas the description of borderline affective instability stresses affective shifts that may be reactive, the description of bipolar affective instability makes no reference to such reactivity.

Interface Between Bipolar Disorder and Borderline Personality Disorders

Delineating the interface between BPD and bipolar disorder has proven complex and challenging. One group of investigators has advocated the position that BPD is a form of affective disorder [6]. This group has asserted that the emotional reactivity in BPD arises from a cyclothymic temperament, which they believe to be a variant of bipolar II disorder. This group has proposed the following definition of a cyclothymic temperament based on two criteria sets. The first includes: (1) hypersomnia vs. decreased need for sleep, (2) introverted self-absorption vs. uninhibited people seeking, (3) taciturn vs. talkative, (4) unexplained tearfulness vs. buoyant jocularity, and (5) psychomotor inertia vs. restless pursuit of activities. The second set includes: (1) lethargy and somatic discomfort vs. eutonia, (2) dulling of senses vs. keen perceptions, (3) slow-witted vs. sharpened thinking, (4) shaky self-esteem alternating between low self-confidence and overconfidence, and (5) pessimistic brooding vs. optimism and carefree attitudes [11]. Based on research with subjects suffering from atypical depression, this group has found that patients with cyclothymic temperaments—35 % of whom were diagnosed with some form of bipolar disorder—were substantially more likely to meet criteria for BPD than subjects who did not have cyclothymic temperaments. Although this study employed standardized clinician administered assessments, its validity is limited by the fact that interviewers administering Axis II assessments were not blind to Axis I diagnosis. It should be noted, moreover, that most of the elements of a cyclothymic temperament do not appear to involve the type of affective shifts described above as typical of BPD.

Additional data suggesting an overlap between BPD and bipolar disorder have come from studies of the prevalence of bipolar disorder in populations with BPD and from studies of mood stabilizing medications. Studies have generally shown higher rates of bipolar disorder in subjects with BPD than in the general population. Studies examining rates of bipolar I disorder in BPD have found rates ranging from 5.6 to 16.1 %; studies examining rates of bipolar II disorder in BPD have found rates ranging from 8 to 19 % [5]. Studies looking at the question of whether BPD precedes the onset of bipolar disorder have been mixed. Two studies have found no significant differences between BPD and comparison subjects in rates of new onset bipolar disorder [12, 13]. However, a large longitudinal study of personality disorders found BPD subjects had a significantly higher rate of new onsets of bipolar subjects in comparison to subjects with other personality disorders (8.2 % vs. 3.1 %) [14].

Studies of mood-stabilizing agents previously found to be effective in treating bipolar disorder have shown that these agents reduce affective symptoms in BPD. Studies have shown that valproic acid is effective in reducing anger and depression in BPD [15] and manic symptoms in bipolar disorder [16]. Research has shown that lamotrigine is effective in reducing anger and overall affective instability in BPD [17], as well as reducing relapses of bipolar depression in bipolar disorder [18]. Research has suggested that oxcarbazepine is effective in reducing affective instability in BPD [19] and manic symptoms in bipolar disorder [20].

Finally, studies have shown that aripiprazole may reduce anxiety, depression, and anger in BPD [21] while reducing manic and depressive symptoms in bipolar disorder [22].

Despite evidence that bipolar disorder and BPD may share clinical features and neurobiologies, some researchers assert that evidence does not support an overlap between the two entities [5]. To begin with, they note that, although there is evidence of increased bidirectional comorbidity between the two disorders, this increase is not any greater for BPD as opposed to other personality disorders. Second, they note that each disorder has a distinct phenomenology. Changes from euthymia to elation or depression to elation are characteristic of bipolar disorder, but not BPD. Additionally, affective changes in BPD are considered reactive to environmental events, but the mood shifts in bipolar disorder are less clearly associated with stressors. Third, these researchers note that the frequency of bipolar disorder in first-degree relatives of BPD probands is not necessarily higher than the frequency of bipolar disorder in the general population. Fourth, they note that the courses of BPD and bipolar disorders differ: unlike BPD, bipolar disorder rarely remits within 2 years. Lastly, they write that there is currently no evidence of overlapping biological factors for the two disorders.

One area where there may be particular overlap between BPD and BD occurs in the rapid cycling experienced by some bipolar patients. The DSM-V defines rapid cycling bipolar disorder as having four mood episodes within a 12-month period [1]. Clinical experience suggests that some bipolar patients will have many more than four episodes during that time. There is evidence that, compared to non-rapid cycling bipolar patients, patients with rapid cycling may share some features of BPD. Rapid cycling bipolar patients may make more suicide attempts and have more comorbidity including substance abuse or dependence, eating disorders, and anxiety disorders [23]. Some authors have gone so far as to propose that the same mechanism may cause both rapid cycling and the affective instability in BPD [24]. Nevertheless, the exact relationship between rapid cycling and the affective instability found in BPD remains unclear.

Studies of Affective Instability in BPD and Bipolar Disorder

Most studies of affective instability in BPD have compared borderline subjects to healthy controls (HCs) or subjects with psychiatric diagnoses other than bipolar disorder. Most studies of affective instability in bipolar disorder have compared bipolar subjects to healthy controls. Current studies of affective instability in BPD and bipolar disorder have employed self-report measures, prospective assessment, or laboratory measures.

Retrospective studies have assessed frequency, intensity, quality of affective changes, and emotion regulation in BPD. One study found that, compared to subjects with other personality disorders, subjects with BPD report more frequent shifts between: euthymia and anxiety, euthymia and anger, and depression and anxiety [25]. This study did not find any difference in the intensity of affective shifts between the two groups.

A second study, assessing emotion dysregulation, found that, even when controlling for overall negative emotions such as depression and anxiety, borderline subjects had more difficulty with emotion regulation, particularly with respect to awareness of emotions and impulsivity [26].

The most recent studies using prospective assessment of affective instability in BPD have used Ecological Momentary Assessment (EMA), involving pencil and pen measures or electronic diaries. EMA has several advantages over retrospective assessment. First, it records information while subjects are in their natural environment. Second, it captures information about immediate or near immediate experiences and thereby minimizes inaccuracies that may occur during retrospective reporting. One study using EMA to compare affective instability in BPD and normal controls found that BPD subjects had significantly more changes in affect from a positive to a negative state [27]. This study was limited in that it covered only a 24-h period. A second study, also covering a 24-h period, used EMA to assess patterns of affective shifts in subjects with BPD and HCs. This study found that BPD patients reported more shifts: (1) between anxiety and sadness and (2) from anxiety to anger [28]. A third study used EMA to assess affective instability in borderline and depressed patients over a 28-day period. This study found that borderline patients reported more significant variability in both positive and negative emotions. Furthermore, borderline patients reported larger increases in sadness, hostility, and fear from one assessment to the next [10].

Laboratory studies examining emotional reactivity in BPD have produced mixed results. Two studies have found that, in response to visual cues, subjects with BPD were no more reactive than either subjects with major depression or healthy controls [29, 30]. But several other studies evaluating affective instability, using both visual and auditory cues, have found BPD subjects to be more emotionally hyperreactive. These studies have measured responsiveness to color slides with different affective valences; videos containing neutral, violent, or abandonment themes; and short stories [31–33]. In general, these studies have found hyperresponsiveness to positive, negative, and neutral stimuli. Of note, the two studies that did not find BPD to be associated with emotional hyperreactivity used inpatient BPD subjects, who may have been affectively blunted by sedating medication [34].

Two laboratory studies have supported the theory that BPD patients have increased difficulty with emotion regulation. One found that, after being instructed to forget a series of words, BPD subjects were more likely than HCs to remember words associated with negative emotional valence [35]. Similarly, a second study found that subjects with BPD were more likely to remember negatively valenced words they had been instructed to forget. In addition, this study found that BPD subjects had more difficulty suppressing attention to aversive irrelevant stimuli [36].

In contrast to BPD, there has been little research on affective instability in bipolar disorder, particularly in euthymic bipolar patients. One study compared affective instability in euthymic bipolar patients and HCs [3]. To measure frequency of affective instability, this study used the Affective Lability Scale (ALS), a 54-item self-report questionnaire measuring affective instability in six dimensions [37]. These dimensions include shifts between euthymia and elation, euthymia and depression,

depression and elation, euthymia and anger, euthymia and anxiety, and depression and anxiety. To measure intensity of affective instability, this study used the Affect Intensity Measure (AIM), a 40-item self-report instrument that measures the intensity of both positive and negative affects [38]. Patients in the bipolar group were predominantly bipolar I (78.8 %). Over half the bipolar subjects (58.7 %) had had psychotic episodes. This study found that, compared to HCs, bipolar patients had higher overall ALS scores and higher scores on all dimensional subscales of the ALS. In addition, bipolar patients had higher overall scores on the AIM.

Laboratory studies have found that compared to healthy controls, normothymic bipolar subjects respond to photos and film clips with higher levels of positive emotion [4, 39]. But there is no evidence that bipolar patients differ from healthy controls in terms of negative emotional reactivity. Specifically, studies have shown no differences in emotional responses of bipolar subjects to negative feedback [40], interpersonal criticism [41], or negative photos [42].

Three studies have directly compared affective instability in BPD and bipolar disorder. The first of these studies compared affective instability in type II bipolar (BPII) disorder, BPD, and other personality disorders (OPD) [43]. This study had four subject groups: subjects with BPD alone ($N=29$); subjects with BPII and another personality disorder, but not BPD ($N=14$); subjects with both BPD and BPII disorder ($N=12$); and subjects with other personality disorders but without BPD or BPII disorder ($N=93$). The study found that patients with BPD had higher overall scores on the ALS than subjects with OPD and that there was a trend toward subjects with BPII having higher overall ALS scores than subjects with OPD. Furthermore, it found that subjects with BPD endorsed more frequent lability on the ALS euthymia-anger subscale. BPII subjects, on the other hand, endorsed more frequent shifts on three ALS subscales: euthymia-elation, euthymia-depression, and elation-depression. This study found an interaction between BPD and BPII for higher scores on the depression-anger subscale. Finally, the study found a trend for patients with BPD to have higher scores on the AIM. Results of this study are limited by several factors. First, all the subjects in the bipolar group had comorbid personality disorders. Second, the study did not directly compare subjects with BPD without BPII disorder and subjects with BPII disorder without BPD.

A second study of affective instability in BPD and BD used a self-report measure, the Affective Lability Questionnaire for Borderline Personality Disorder (ALQ-BPD), to compare affective instability in college students with elevated bipolar and borderline features. Subjects in the study consisted of 818 undergraduates at a state university [44]. The study classified subjects as having elevated BPD features if they had scores on the Personality Assessment Inventory Borderline Scale (PAI-BOR) [45] that were two standard deviations or higher above the PAI-BOR mean score for the study sample. The study classified the subjects as having elevated features of BD if they had scores on the Personality Assessment Inventory Mania scale (PAI-MAN) [45] that were two standard deviations or higher above the sample mean for the PAI-MAN. Subjects could not have elevated features of both BPD and BD. Twenty-three subjects met study criteria for elevated BPD features; 21 subjects met study criteria for elevated BD features. Two subjects were excluded

because they had elevated features of both disorders. Subjects with elevated BPD features endorsed more *frequent* affective changes in 7 of 9 affective dimensions of the ALQ-BPD. These included shifts between euthymia-depression, euthymia-anger, euthymia-anxiety, depression-anxiety, anxiety-depression, anger-depression, and depression-anger. Subjects with elevated borderline features endorsed more *intense* affective shifts in 2 of 9 dimensions: euthymia-depression and anxiety-depression. Composite subscale scores for both frequency and intensity were higher for subjects with elevated borderline features.

Results of this study suggest clear differences in affective instability between BPD and bipolar disorder, but the study had several important limitations. Although subjects in the study appeared to have clear elevations in BPD or bipolar features, they were not actually diagnosed with any psychiatric disorder. Consequently, the study did not distinguish between different types of bipolar disorder. Second, the study did not control for severity of symptoms. Third, the study did not assess such factors as medication status, severity of illness, and comorbidity aside from BPD and BD. Finally, because the ALQ-BPD measures affective instability only over the last week, it may not be an accurate indication of affective instability as a trait for these disorders.

One study has used a clinician administered instrument, the Affective Lability Interview for Borderline Personality Disorder (ALI-BPD), to compare affective instability in BPD and BD [46]. Additionally, this study assessed affective instability using the ALS and the AIM. Subjects in the study were 29 subjects with BPD and 25 subjects with BPII disorder. The study assessed subjects diagnostically using the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I), the Diagnostic Interview for DSM-IV Personality Disorders (DIPD-IV), and the Revised Diagnostic Interview for Borderlines (DIB-R). Subjects diagnosed as borderline met DSM-IV criteria for BPD and had DIB-R scores of 8 or higher. Subjects diagnosed as type II bipolar met DSM-IV criteria for this disorder. The study excluded potential subjects with comorbid BPD and BPII.

As with results using the ALQ-BPD, results of this study suggested clear differences in affective instability between bipolar disorder and BPD. On the ALS, BPII subjects reported significantly more frequent shifts between euthymia and elation. BPD subjects reported more frequent shifts between depression and anxiety. BPII subjects had higher scores on the positive emotion subscale of the AIM. On the ALI-BPD, bipolar II subjects reported more frequent shifts in dimensions traditionally considered more bipolar: shifts between euthymia and elation and shifts between depression and elation. Borderline subjects reported more frequent shifts between euthymia and anger, between depression and anxiety, and between anxiety and depression. BPII subjects reported more intense shifts between euthymia and elation and between depression and elation. Borderline subjects reported more intense shifts between euthymia and anxiety, euthymia and anger, depression and anxiety, and anxiety and depression. Composite subscale scores for intensity and frequency for those affective dimensions considered more typically borderline—euthymia-anxiety, euthymia-anger, depression-anxiety, and anxiety-depression—were higher for subjects in the borderline group.

This study, too, had several limitations. First, the size of the study sample was relatively small. Second, subjects in the BPD group had Global Assessment of Functioning (GAF) scores that were 9 points lower than subjects in the bipolar group. Third, most of the subjects in the study were taking psychotropic medications, which may influence affective instability. Fourth, like the ALQ-BPD, the ALI-BPD is largely a state measure and therefore may not provide valid information on affective instability as a trait.

Overall, results of current studies suggest that the affective instability in BPD and bipolar disorder has different profiles. Not surprisingly the affective instability in bipolar disorder involves more elation. The affective instability in BPD, in contrast, appears to consist more of affective shifts involving anxiety, depression, and anger. The differences between the two groups appear to include differences in both frequency and intensity.

Neural Correlates of Affective Instability in BPD and Bipolar Disorders

If the affective instability in BPD and BD is different, then presumably the affective instability in each has a different neurobiology. As noted above, there are no studies comparing the neurobiology of affective instability in BPD and BD. There are, however, multiple studies that provide clues about the neurobiology of affective instability in BPD and BD by examining the emotion processing and regulation in each disorder. Studies of affective processing in both BPD and BD have shown that this processing differs from affective processing in healthy controls. Interpretation of these studies for BD is complicated by two factors. First, these studies are diagnostically heterogeneous, including bipolar I and bipolar II patients. Second, the studies include subjects in states of euthymia, mania, and depression. Overall, these studies have found abnormalities of amygdala activation that vary by mood state. In addition, studies have suggested that there is mood-independent hypoactivation of the ventrolateral prefrontal cortex (VLPFC)—a structure responsible for regulation of the intensity of emotional responses, cognitive responses to negative emotions, and overall emotional integration—and that this may be a trait marker of BD [47].

Studies of BPII subjects may be particularly relevant for comparison with BPD because symptoms and associated features of bipolar II disorder appear to more closely resemble BPD. Two studies have used fMRI to examine emotion processing in unmedicated depressed BPII subjects. Both studies have employed emotional face activation paradigms. One study found reduced activation in the bilateral VLPFC and the right amygdala [48]. A second study found decreased activation of posterior cortical midline structures (precuneus, cingulated cortex, and medial parietal cortex) [49]. Notably, no studies have examined emotion processing in euthymic BPII subjects.

Studies of neural correlates of emotional processing in BPD have used presentation of emotional faces, aversive scenes, or memories of negative life events as activation paradigms [50–56]. Most of these studies showed enhanced amygdala activity in BPD, suggesting this may be a trait marker for the disorder [50–53, 55, 56]. Collectively, these studies have shown enhanced activation of multiple prefrontal structures: the middle and inferior temporal cortical areas, anterior and posterior cingulate cortices (ACC and PCC), insula, and medial and inferolateral prefrontal cortical areas. Overall, current neuroimaging research suggests that affective processing in BPD differs from that in BD in that it involves more widespread abnormalities in cortical structures involved in affect regulation, as well as abnormalities in the amygdala, a structure involved in affect generation.

Clinical Illustrations

Several case examples may illustrate the differences between affective instability in BPD and bipolar disorder, as well as the complexity of affective instability in each.

Case 1

The patient was a 28-year-old female admitted to an inpatient psychiatric unit for increased depression and suicidality. She carried a diagnosis of atypical bipolar disorder. She reported chronic fluctuating levels of depression. She reported shifts between feeling depressed and feeling severely anxious several times per day. She had a history of episodes of feeling both depressed and agitated at the same time. She had no history of affective shifts involving elation. She had received trials of multiple mood stabilizers, including valproic acid and lithium. None of these had provided relief from her symptoms. She had also received trials of multiple SSRIs, venlafaxine, and tricyclic antidepressants with only slight and transient improvement in depression and no improvement in anxiety. She stated that benzodiazepines were most helpful in reducing her dysphoria, but tended to provide only partial relief some of the time. At the time of admission, her medications consisted of lamotrigine, quetiapine, duloxetine, and lorazepam. She had an extensive history of childhood physical and verbal abuse. During her hospital course, staff noticed that she experienced frequent fluctuations in anxiety and distress. Often, such fluctuations occurred when she felt neglected by her family. The patient was focused on the desire for changes in her pharmacotherapy to treat her affective shifts and requested a consult for electroconvulsive therapy when told that medication changes were unlikely to reduce her symptoms significantly. Staff responded by suggesting the patient to focus on developing distress tolerance skills.

In this case, the patient presents with a diagnosis of bipolar, but affective instability more consistent with BPD. The patient had no history of mood instability

involving elation and no history of mood instability that had responded to mood stabilizers. Her affective instability had a strong reactive component. As is often the case in borderline patients misdiagnosed with bipolar disorder, her treatment expectations centered on pharmacotherapy or other biological modalities instead of psychological treatments.

Case 2

The patient was a 24-year-old female who presented for treatment with a history of anxiety, stimulant abuse, and major depression. She reported frequent swings between euthymia and anxiety. She became distressed whenever a romantic relationship ended and tended to try to find a new romantic partner as soon as possible. She had difficulty tolerating frustration and often became angry and verbally abusive when she felt mistreated by family or friends. She had a history of agitation, increased difficulty falling asleep, and difficulty remaining asleep when being treated with antidepressants during the late spring and early summer. Beginning in her third year of treatment, the patient experienced a dramatic increase in irritability and anxiety. When frustrated, she assaulted her boyfriend and family members. This increase in irritability was not associated with any situational factors, but ultimately led to a breakup with her boyfriend. She required hospitalization because of concern about her ability to control her assaultiveness. During the hospitalization, she was started on Depakote, which provided some relief of her agitation and irritability. Upon discharge, the patient's inpatient team referred her for outpatient Dialectical Behavior Therapy (DBT). Over the next 3 years, she continued to have intermittent episodes of severe agitation, dysphoria, and irritability. These typically involved difficulty falling and remaining asleep. During these episodes the patient often became explosive, destroying things and being verbally abusive to family and friends. She had no further depressive episodes and rarely complained of any depressed mood. After trials of multiple mood stabilizers, her irritability and dysphoria responded to a regimen of lithium and oxcarbazepine. Even after these symptoms had remitted, however, she continued to display a tendency to become distressed whenever she felt alone.

This case illustrates the potential for bipolar and borderline symptoms—including mood instability—to overlap. This patient presented with symptoms characteristic of BPD. She had fluctuating and often high levels of anxiety, was quick to anger when frustrated, and had difficulty tolerating being alone. Her bipolar symptoms emerged during an intense and unstable relationship with a romantic partner and contained exaggerated elements of earlier BPD symptoms. One of these elements was the intensification of her anxiety and her irritability. But her bipolar symptoms ultimately become endogenous and did not remit even as the stress around her subsided. DBT was only modestly effective in relieving her affective symptoms, and her mood instability did not improve until she responded to

mood stabilizers. But even after her dysphoric manic symptoms had significantly diminished, she continued to demonstrate emotional reactivity in response to separation. Thus, patients with comorbid bipolar disorder and BPD may continue to display affective instability characteristic of BPD even after their active bipolar symptoms are in full or partial remission.

Clinical Implications and Treatment

The different profiles of affective instability have implications for both diagnosis and treatment of BPD and BD. If affect instability differs substantially between the two disorders, this suggests that careful assessment of affective instability may provide important diagnostic information enabling clinicians to distinguish between the two disorders. Such assessment may be particularly important in view of the apparent tendency of clinicians to overdiagnose bipolar disorder in patients with BPD [57]. More accurate diagnosis of BPD may, in turn, steer clinicians away from overreliance on pharmacotherapy instead of evidence-based psychotherapies [58–61] to achieve affective stabilization.

Pharmacotherapy may be useful in treating affective instability in BPD and bipolar disorder (Table 5.2). As noted above, multiple studies suggest, either directly or indirectly, that pharmacotherapy may reduce affective instability in BPD. Two placebo-controlled studies have directly assessed the psychopharmacologic response of affective instability in BPD. The first found that, compared to placebo, fluvoxamine 150–250 mg/day was modestly effective in reducing rapid mood shifts in BPD as measured by the Borderline Personality Disorder Severity Index [62]. The second found lamotrigine 25–225 mg/day (mean dose 107 mg/day) was also modestly effective in reducing affective instability as measured by the Zanarini Rating Scale for Borderline Personality Disorder [17]. Other studies have suggested aripiprazole, valproic acid, and topiramate may be effective in ameliorating affective instability by finding these agents effective in reducing anger or anxiety in borderline patients [17, 23, 63]. There is abundant evidence that mood-stabilizing

Table 5.2 Medications

Medication	BPD	BD
Fluvoxamine	↓ Rapid mood shifts (moderate effect)	
Lamotrigine	↓ Affective instability (moderate effect)	
Aripiprazole Valproic acid Topiramate	↓ Anger or anxiety	
Lithium Valproic acid Aripiprazole		↓ Mood instability

agents such as lithium, valproic acid, and aripiprazole are effective in reducing mood instability in bipolar disorders [20, 24]. But there is no research showing that pharmacotherapy reduces the affective instability that appears to exist in even euthymic states in bipolar disorder.

Although no evidence-based psychotherapies for borderline personality disorder or bipolar disorder target affective instability directly, all of them can be interpreted as having affective instability as indirect targets. Dialectical Behavioral Therapy (DBT) includes a module on emotion regulation [58]. Mentalization-Based Therapy (MBT) may ameliorate affective instability by reducing the distress borderline patients experience as a result of disruptions in attachment [59]. Transference-Focused Psychotherapy (TFP) for BPD may reduce affective instability by helping patients to tolerate contradictory affective states centered on positive and negative emotions [60]. Finally, Schema-Focused Therapy (SFT) may alleviate affective instability by teaching emotion regulation skills and working to reduce the frequency of switching between extreme cognitive/affective states (schema modes) in borderline patients [61].

To date, there has been little research directly examining the effect of evidence-based psychotherapies on affective instability in BPD. But several outcome studies of measuring overall symptom severity have suggested indirectly that MBT, DBT, and SFT may reduce affective instability in this disorder [64–66]. Such studies have also suggested, however, that DBT and TFP may not be any more effective than supportive psychotherapy in reducing factors such as anger that may be closely associated with affective instability [64]. One study directly assessed the effect of DBT on affective instability in BPD [67]. This study found that use of DBT skills correlated significantly with reductions in affective instability over 1 year of DBT treatment.

Psychotherapies applied to bipolar disorder include Cognitive Behavioral Therapy (CBT), psychoeducation, Family-Focused Therapy (FFT), and Interpersonal and Social Rhythm Therapy (ISRT) [68]. These psychotherapies might reduce affective instability in a number of ways: (1) improving emotional self-regulation skills; (2) enhancing medication compliance; (3) improving social supports; (4) promoting balanced and less pessimistic attitudes toward self in relation to illness; (5) enhancing communication, family relationships, and overall social skills; and (6) improving ability to identify and intervene with early relapses [69]. To date, however, there has been no research studying the effectiveness of any of these treatments on affective instability. One recent pilot study examined the effectiveness of DBT-based psychoeducational group therapy on emotion regulation in patients with bipolar disorder [70]. This study found no differences in self-reported emotion regulation measures for patients treated with this group therapy in comparison to patients in a wait list control group. However, a second recent pilot study found that mindfulness-based cognitive therapy significantly improved emotion regulation in bipolar patients [71].

Conclusions

Affective instability is a complex concept with multiple dimensions. It is important to distinguish affective instability from affective lability, the temperamental vulnerability to experience rapid and strong affective changes, and from mood instability, which applies to more sustained affective states and is more applicable to shifts into depression or euphoria characteristic of bipolar disorder. Affective instability appears to be a significant feature of both BPD and bipolar disorder, even in euthymic bipolar patients. Characterizing the differences in affective instability between BPD and BD is an important tool for distinguishing between these disorders.

Most research on affective instability in BPD and BD has used retrospective data and has dealt with the first three components of affective instability mentioned above. Existing studies suggest affective instability in each disorder has different characteristics: subjects with BPD tended to have more shifts involving anger, depression, and anxiety; subjects with BD have more shifts involving euphoria. Research on the neurobiology of affective instability in BPD and BD is limited, but suggests that this neurobiology may differ between the two disorders. Whereas affective instability in BD appears to involve only cortical structures implicated in affect regulation, affective instability in BPD appears to involve more of these cortical structures as well as the amygdala.

Research on treatments that might alleviate affective instability in BPD and bipolar disorder has been limited. Multiple psychopharmacologic agents, particularly mood stabilizers, seem likely to reduce affective instability in BPD and bipolar disorder. However, only two studies have directly assessed the effectiveness of pharmacotherapy in reducing affective instability in BPD, and there are no studies of pharmacotherapy of affective instability in euthymic bipolar patients. Although there is evidence that multiple psychotherapies reduce BPD symptoms, only one study has shown that psychotherapy might effectively treat affective instability in BPD. There is no direct evidence that any psychotherapy reduces affective instability in BD.

In conclusion, further research is needed to improve the understanding of affective instability in both BPD and BD. To begin with, this research should include ecological momentary assessments of bipolar patients, as well as expanded retrospective assessments using validated clinical instruments in patient populations. Second, this research should directly compare the neurobiology of affective instability in borderline and bipolar patients. Finally, the lack of direct evidence that psychosocial and biological treatments reduce affective instability in both BPD and bipolar disorder highlights the need for more research in this area.

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013.
2. Sanislow CA, Grilo CM, McGlashan TH. Factor analysis of the DSM-III-R borderline personality disorder criteria in psychiatric inpatients. Am J Psychiatry. 2000;157:1629–33.

3. Henri C, Van den Bulke D, Bellivier F, Roy I, Swendsen S, M'Bailara K, et al. Affective lability and affect intensity as core dimensions of bipolar disorders during euthymic period. Psychiatry Res. 2008;159:1–6.
4. M'Bailara K, Demotes-Mainard J, Swendsen J, Mathieu F, Leboyer M, Henry C. Emotional hyper-reactivity in normothymic bipolar patients. Bipolar Disord. 2009;11:63–9.
5. Paris J, Gunderson J, Weinberg I. The interface between borderline personality disorder and a bipolar spectrum disorders. Compr Psychiatry. 2007;48:145–54.
6. Akiskal HS. Demystifying borderline personality disorder: critique of the concept and unorthodox reflections on its natural kinship with the bipolar spectrum. Acta Psychiatr Scand. 2004;110:401–7.
7. Renaud S, Corbalan F, Beaulieu S. Differential diagnosis of bipolar disorder type II and borderline personality disorder: analysis of the affective direction. Compr Psychiatry. 2012;53: 952–61.
8. Links PS, Rahel E, Marnin JH, Nisenbaum R. Elements of affective instability associated with suicidal behavior in patients with borderline personality disorder. Can J Psychiatry. 2008;53: 112–6.
9. Larsen R. The stability of mood variability: a spectral analytic approach to daily mood assessments. J Pers Soc Psychol. 1987;52:1195–204.
10. Trull TJ, Solhan MB, Jahng S, Wood PK, Piaseci TM, Watson D. Affective instability: measuring a core feature of borderline personality disorder with ecological momentary assessment. J Abnorm Psychol. 2008;117:647–61.
11. Perugi G, Toni C, Travierso MC, Akiskal HS. The role of cyclothymia in atypical depression: toward a data-based reconceptualization of the borderline bipolar II connection. J Affect Disord. 2003;73:49–57.
12. Links PS, Heslegrave RJ, Milton JE, Van Reekum R, Patrick J. Borderline psychopathology and recurrences of clinical disorders. J Nerv Ment Dis. 1995;183:582–6.
13. Zanarnini MC, Frankenburg FR, Hennen J, Reich DB, Silk K. Axis I comorbidity in patients with borderline personality disorder: 6-year follow-up and prediction of time to remission. Am J Psychiatry. 2004;161:2108–14.
14. Gunderson JG, Weinberg I, Daversa MT, Kuepenbender KD, Zanarini MC, Shea MT, et al. Am J Psychiatry. 2006;163:1173–8.
15. Frankenburg FR, Zanarini MC. Divalproex sodium treatment of women with borderline personality disorder and bipolar II disorder: a double-blind placebo-controlled pilot study. J Clin Psychiatry. 2002;63:442–6.
16. Pope HG, McElroy SL, Keck PE, Hudson JL. Valproate in the treatment of acute mania. A placebo-controlled study. Arch Gen Psychiatry. 1991;48:62–8.
17. Reich DB, Zanarini MC, Bieri KA. A preliminary study of lamotrigine in the treatment of affective instability in borderline personality disorder. Int Clin Psychopharmacol. 2009;24: 270–5.
18. Goodwin GM, Bowden CL, Calabrese JR, Grunze H, Kasper S, White R, Green P, Leadbetter R. A pooled analysis of 2 placebo-controlled 18-month trials of lamotrigine and lithium maintenance in bipolar I disorder. J Clin Psychiatry. 2004;65:432–41.
19. Bellino S, Paradiso E, Bogetto F. Oxcarbazepine in the treatment of borderline personality disorder: a pilot study. J Clin Psychiatry. 2005;66:1111–5.
20. Mazza M, DiNicola M, Martinotti G, Taranto C, Pozzi G, Conte G, et al. Oxcarbazepine in bipolar disorder. Expert Opin Pharmacother. 2007;8:649–56.
21. Nickel MK, Muehlbacher M, Nickel C, Kettler C, Gil FP, Bachler E, et al. Aripiprazole in the treatment of borderline personality disorder: a double-blind, placebo-controlled study. Am J Psychiatry. 2006;163:833–8.
22. Keck PE, Marcus R, Tourkodimitris S, Ali M, Liebeskind A, Saha A, Ingenito G. A placebo-controlled, double-blind study of the efficacy and safety of aripiprazole in patients with acute bipolar mania. Am J Psychiatry. 2003;160:1651–8.
23. MacKinnon DF, Zandi PP, Gershon E, Nurnburger JI, Reich T, DePaolo JR. Rapid switching of mood in families with multiple cases of bipolar disorder. Arch Gen Psychiatry. 2003;60:921–8.

24. Mckinnon DF, Pies R. Affective instability as rapid cycling: theoretical and clinical implications for borderline personality and bipolar spectrum disorders. Bipolar Disord. 2006;8:14.
25. Koenigsberg HW, Harvey PD, Mitropolou V, Schmiedler J, New AS, Goodman M, Silverman JM, Serby M, Schopick F, Siever LJ. Characterizing affective instability in borderline personality disorder. Am J Psychiatry. 2002;159:784–8.
26. Glenn CR, Klonsky ED. Emotion dysregulation as a core feature of borderline personality disorder. J Pers Disord. 2009;23:20–8.
27. Ebner-Priemer UW, Kuo J, Kleindienst N, Welch SS, Reisch T, Reinhard I, et al. State affective instability in borderline personality disorder assessed by ambulatory monitoring. Psychol Med. 2007;37:961–70.
28. Reisch T, Ebner Priemer UW, Tschacher W, Bohus M, Linehan MM. Sequences of emotions in patients with borderline personality disorder. Acta Psychiatr Scand. 2008;118:42–8.
29. Renneberg B, Heyn K, Gebhard R, Bachmann S. Facial expression and emotions in borderline personality disorder. J Behav Ther Exp Psychiatry. 2005;36:183–96.
30. Herpertz SC, Kunert HJ, Schwenger UB, Sass H. Affective responsiveness in borderline personality disorder: a psychophysiologic approach. Am J Psychiatry. 1999;156:1550–6.
31. Jennings ME. Emotion regulation in borderline personality disorder: a psychophysiological examination of emotional responding and recovery. Dissert Abstr Int. 2004;64:5219B.
32. Herpertz S, Gretzer A, Muhlbauer V, Steinmeyer EM, Sass H. Experimental proof of affect dysregulation in patients with self-destructive behavior. Nervenarzt. 1998;69:410–8.
33. Conrad SD, Morrow RS. Borderline personality organization, dissociation, and willingness to use force in intimate relationships. Psychol Men Masc. 2000;1:37–48.
34. Sansone RA, Sansone LA. Emotional hyper-reactivity in borderline personality disorder. Psychiatry. 2010;7:16–20.
35. Korfine L, Hooley JM. Directed forgetting of emotional stimuli in borderline personality disorder. J Abnorm Psychol. 2000;109:214–21.
36. Domes G, Winter B, Schnell K, Vohs K, Fast K, Herpertz SC. The influence of emotions on inhibitory functioning in borderline personality disorder. Psychol Med. 2006;36:1163–72.
37. Harvey PD, Greenberg BR, Serper MR. The affective lability scale: development, reliability, and validity. J Clin Psychol. 1989;45:786–93.
38. Larsen RJ, Diener E, Emmons RJ. Affect intensity and reactions to daily life events. J Pers Soc Psychol. 1986;51:803–14.
39. Gruber J, Harvey AG, Purcell A. What goes up can come down? A preliminary investigation of emotion reactivity and recovery in bipolar disorder. J Affect Disord. 2011;133:457–66.
40. Ruggero C, Johnson SL. Reactivity to a laboratory stressor among individuals with bipolar I disorder in full or partial remission. J Abnorm Psychol. 2006;115:539–44.
41. Cuellar A, Johnson SK, Ruggero C. Affective reactivity in response to criticism in remitted bipolar disorder: a laboratory analog of expressed emotion. J Clin Psychol. 2009;65:925–41.
42. Sutton SK, Johnson SL. Hypomanic tendencies predict lower startle magnitudes during pleasant pictures. Psychophysiology. 2002;S39:80.
43. Henry C, Mitropolou V, New AS, Koenigsberg HW, Silverman J, Siever LJ. Affective instability and impulsivity in borderline personality and bipolar II disorders: similarities and differences. Psychiatry Res. 2001;35:307–12.
44. Reich DB, Zanarini MC, Hopwood CJ, Thomas KM, Fitzmauric G. Comparison of affective instability in borderline personality disorder using a self-report measure. J Pers Ment Health. 2014;8:143–50.
45. Morey LC. The personality assessment interview. Lutz: Psychological Assessment Resources; 1991.
46. Reich DB, Zanarini MC, Fitzmaurice GM. Affective lability in bipolar disorder and borderline personality disorder. Compr Psychiatry. 2012;53:145–54.
47. Townsend J, Altshuler LL. Emotion processing and regulation in bipolar disorder: a review. Bipolar Disord. 2012;14:326–39.
48. Vizueta N, Rudie HD, Townsed JD, Torrisi S, et al. Regional fMRI hypoactivation and altered functional connectivity during emotion processing in unmedicated depressed patients with bipolar II disorder. Am J Psychiatry. 2012;169(8):831–40.

49. Marchand WR, Lee JN, Garn C, Thatcher J, Gale P, Kreitschitz S, Johnson S, Wood N. Abnormal emotional processing in posterior cortical midline structures in bipolar II depression. Prog Neuropsychopharmacol Biol Psychiatry. 2011;35:1729–37.
50. Herpertz SC, Dietrich TM, Wenning B, Krings T, Erberich SG, Willmes K, Thron A, Sass H. Evidence of abnormal amygdala functioning in borderline personality disorder: a functional MRI study. Biol Psychiatry. 2001;50:292–8.
51. Donegan NH, Sanislow CA, Blumberg HP, Fulbright RK, Lacadie C, Skudlarski P, et al. Amygdala hyperreactivity in borderline personality disorder: implications for emotional dysregulation. Biol Psychiatry. 2003;54:1284–93.
52. Beblo T, Driessen M, Mertens M, Wingenfeld K, Piefke M, Rullkoetter N, et al. Functional MRI correlates of the recall of unresolved life events in borderline personality disorder. Psychol Med. 2006;36:845–56.
53. Minzenberg MJ, Fan J, New AS, Tang CY, Siever LJ. Frontal-limbic dysfunction in response to facial emotion in borderline personality disorder: an event-related fMRI study. Psychiatry Res. 2007;155:231–43.
54. Guitart-Masip M, Pascual JC, Carmona S, Hoekzema E, Berge D, Perez V, et al. Neural correlates of impaired emotional discrimination in borderline personality disorder: an fMRI study. Prog Neuropsychopharmacol Biol Psychiatry. 2009;33:1537–45.
55. Koenigsberg HW, Siever LJ, Lee H, Pizzarello S, New AS, Goodman M, et al. Neural correlates of emotion processing in borderline personality disorder. Psychiatry Res. 2009;172: 192–9.
56. Schulze L, Domes G, Kruger A, Berger C, Fleischer M, Prehn K, et al. Neuronal correlates of cognitive reappraisal in borderline patients with affective instability. Biol Psychiatry. 2011;69: 564–73.
57. Zimmerman M, Ruggero CJ, Chelminski I, Young D. Psychiatric diagnoses in patients previously overdiagnosed with bipolar disorder. J Clin Psychiatry. 2010;71:26–31.
58. Rinne T, van den Brink W, Wouters L, van Dyck R. SSRI treatment of borderline personality disorder: a placebo-controlled clinical trial for female patients with borderline personality disorder. Am J Psychiatry. 2002;159:2048–54.
59. Loew TH, Nickel MK, Muehlbacker M, Kaplan P, Nickel C, Kettler C, et al. Topiramate treatment for women with borderline personality disorder: a double-blind, placebo-controlled study. J Clin Psychopharmacol. 2006;26:61–6.
60. Linehan MM. Skills training manual for treating borderline personality disorder. New York: The Guilford Press; 1993.
61. Bateman AW, Fonagy P. Psychotherapy of borderline personality disorder. New York: Oxford University Press; 2004.
62. Clarkin JF, Foelsch PA, Levy KN, Hull JW, Delaney JC, Kernbery OF. The development of a psychodynamic treatment for borderline personality disorder: a preliminary study of behavioral change. J Pers Disord. 2001;15:487–95.
63. Young JE, Klosko JS, Weishaar ME. Schema therapy: a practitioner's guide. New York: The Guilford Press; 2003.
64. Clarkin JF, Levy KN, Lenzenweger MF, Kernberg OF. Evaluating three treatments for borderline personality disorder: a multiwave study. Am J Psychiatry. 2007;164:922–8.
65. Batemen A, Fonagy P. Randomized control trial of outpatient mentalization-based treatment versus structured clinical management for borderline personality disorder. Am J Psychiatry. 2009;166:1355–64.
66. Giesen-Bloo J, van Dyck R, Spinhoven P, van Tilburg W, Dirksen C, van Asselt T, et al. Outpatient psychotherapy for borderline personality disorder. Arch Gen Psychiatry. 2006; 63:649–58.
67. Stepp SD, Epler AH, Jahng S, Trull TJ. The effect of dialectical behavior therapy skills use on borderline personality disorder features. J Pers Disord. 2008;22:549–63.
68. Geddes JR, Miklowitz DJ. Treatment of bipolar disorder. Lancet. 2013;381:1672–82.

69. Miklowitz DJ, Scott J. Psychosocial treatments for bipolar disorder; cost effectiveness, mediating mechanisms, and future directions. Bipolar Disord. 2009;11 Suppl 2:110–22.
70. Van Dijk S, Jeffrey J, Katz MR. A randomized pilot study of dialectical behavior therapy skills in a psychoeducational group for individuals with bipolar disorder. J Affect Disord. 2013;145:386–93.
71. Ives-Deliperi VL, Howells F, Stein DJ, Meintjes EM, Horn N. The effects of mindfulness-based cognitive therapy in patients with bipolar disorder: a controlled functional MRI investigation. J Affect Disord. 2013;150:1152–7.

Chapter 6
Bipolar Illness Versus Borderline Personality: Red Skies Versus Red Apples

S. Nassir Ghaemi and Sergio Barroilhet

Introduction

The differential diagnosis of bipolar illness and borderline personality is important, controversial, and difficult. Some claim that bipolar illness is overdiagnosed and that borderline personality is underdiagnosed [1]. Others claim the reverse [2]. Those who argue that bipolar illness is overdiagnosed often assert that those patients instead have borderline personality [1]. Others claim the reverse [2].

The most common approach to this controversy is to focus on the overlap between the syndromes and then to assert than one merely represents the other [2, 3]. This attitude is abetted by the DSM nosology, which produces overlap in symptoms between many syndromes. It would make sense to focus on areas of difference, if indeed these are different conditions.

In this review, we will examine the scientific evidence for overlap and difference between bipolar illness and borderline personality and seek to come to conclusions about whether they are valid, independent conditions and in what ways they are similar to, or different from, each other as illness entities.

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"Disorder" Is Meaningless

To begin to appreciate the differences between borderline personality and bipolar illness, we would start with our refusal to use the word "disorder." The term is meaningless and vague, and it is meant to be so. It was invented with DSM-III in 1980 as a means of representing the biopsychosocial eclecticism which was the theoretical basis of DSM-III [4]. The proponents of that radical change in psychiatric nosology began with a medical paradigm: the "neo-Kraepelinian" researchers who validated about a dozen diagnoses in the original Research Diagnostic Criteria (RDC) [5] saw those conditions as mainly biological (such as schizophrenia, bipolar illness, unipolar depression, sociopathy, obsessive-compulsive anxiety, panic attacks, alcohol and substance abuse). Borderline personality was not on the list, and the term "disorder" was not used. In the 2 years between the publication of RDC in 1978 and the publication of DSM-III in 1980, about 150 other diagnoses were added to the dozen in the RDC [6]. It is a matter of common sense that 150 diseases were not suddenly discovered in those 2 years when Jimmy Carter was president. Instead, the 150 other labels were added by the American Psychiatric Association (APA) for nonscientific purposes [6]. Various interest groups, especially psychoanalysts who were powerful at the time in the profession, wanted to make sure that their labels were included for many reasons: insurance payment, teaching ability, professional prestige, among others [7]. But scientific validity did not exist for the majority of those conditions. Borderline personality disorder was part of that group.

To break with the psychoanalytic commitment of DSM-II, the leaders of DSM-III decided to claim to be "atheoretical" [7]. Under the political pressure of multiple groups, including the psychoanalytic establishment of the APA, they also were unwilling to differentiate diagnoses that were "endogenous," or biologically based diseases, from "exogenous," or psychosocially caused conditions [7]. They rejected the neo-Kraepelinian view that at least the major psychoses—schizophrenia and manic depression—should be termed biological diseases. Instead, the term "disorder" was employed as a catch-all diagnostic label, presumably to avoid the implication that any label should be interpreted from any particular etiological point of view [7].

While this perspective might have had some rationale for conditions whose nature was unknown, it had the unfortunate consequence of implying an *ontological equality* to all DSM diagnoses, which means that uninformed consumers of the DSM might conclude that all diagnoses are similar to each other in their causes and origins and natures. Schizophrenia is a similar thing to feeling sad after a divorce (adjustment "disorder"). Manic-depressive disease is a similar thing to having changes in your personality after you have been sexually abused for years.

Of the many harms that DSM-III and DSM-IV have caused, one of the worst is the implied ontological equality of all diagnoses, which is part of the reason why clinicians have become confused about two conditions, borderline personality and bipolar illness, which are utterly different.

The historical contrast is instructive: bipolar illness, derived from manic-depressive insanity, is a concept that had 150 years of history, back to mid-nineteenth century France, at least [8] (even more if one accepts the descriptions of mania and melancholia dating to ancient Rome and Greece [9]). Borderline personality was invented in the late 1960s by psychoanalysts [10]. One concept has over a century of biological and clinical research that led to its inclusion in DSM-III. The other concept was included based on the beliefs of American psychoanalysts, with little scientific evidence regarding its validity.

Red Skies Versus Red Apples: Disease Processes Versus Clinical Pictures

This is not to say that borderline personality and bipolar illness have nothing in common. Some cases of schizophrenia and anxiety after divorce also have symptoms in common (e.g., anxiety). The question is, rather, are the similarities between borderline personality and bipolar illness central to those conditions or peripheral and secondary features of those conditions?

The sky can be red; apples are red. So they have redness in common. But being red is not a central feature to the nature of skies, nor to the nature of apples. A sky is a geological fact; an apple is a fruit. They are quite different as things, in their categories of being, in their ontologies. Such is the case, too, with borderline personality and bipolar illness.

Here, a basic diagnostic distinction, rejecting the DSM-eclectic notion of "disorder," is needed. We go back to Kraepelin and traditional German nosology and distinguish between *disease processes* (krankheitsprozesen) and *clinical pictures* (zustandbilden) [11]. All valid psychiatric diagnoses are clinical pictures; some of them are also disease processes. The valid RDC psychiatric diagnoses (not DSM-III/DSM-IV, which is mostly invalid) consist of clinical pictures; some of them are also disease processes. To the extent that borderline personality represents a replicable, stereotypic syndrome—with a specific phenomenology and course and even some biological correlates and treatment outcomes—it can be deemed a scientifically validated clinical picture [12]. This does not make it a disease process, however. Disease processes tend to have biological etiologies and pathogenesis. Clinical pictures, like borderline personality or anxiety after divorce, tend to have psychological and social etiologies and pathogenesis. (Of course there are biological correlates to all psychological states, but this is a trivial fact [4]; in contrast, in disease processes, biological abnormalities are autonomous in their nature, such as with the ventricular enlargement of schizophrenia).

Bipolar illness is a disease process; borderline personality is a clinical picture, not a disease process. The first has a purely biological etiology and pathogenesis; the second has a mostly social and psychological etiology and a mostly psychological pathogenesis. They are completely different in etiology and pathogenesis; they are superficially similar in some symptoms. They are as different as the sky and an apple and as similar as red skies and red apples.

Hypomania is not a Completely Different Entity Than Mania

Attempts have been made to rescue the "disorder" concept from its vagueness; the most common view is that it represents "harmful dysfunction" [13]. On this perspective, borderline personality is diagnosed when it becomes harmful to the person (a value judgment) and leads to functional impairment (a value judgment). So too with bipolar illness, which is why the leaders of DSM have been so adamant to oppose the concept of a bipolar spectrum [14], in which mild and functional manic and depressive symptoms occur. It is also the reason why proponents of borderline personality are so obsessed with the concept of type II bipolar illness [1], namely, hypomania alternating with depression. By definition, hypomania is an anomaly in the DSM ideology: it is the only major DSM diagnosis which is not harmful and not dysfunctional.

On the twisted logic of "disorder," then, hypomania is not a mental condition. This is also a reason why so many DSM nosologists have been upset about allowing the diagnosis of type II bipolar illness [15]. They, and borderline experts, act as if type II bipolar illness is categorically and essentially different than type I. They take this view because they have accepted wholesale the false notion of "disorder," and they cannot accept the medical fact that many, if not most, illnesses have mild variations, as well as severe. There is no essential difference between type II and type I bipolar illness—genetically [16] or biologically [17, 18] or etiologically [19] or pathogenetically [20] or even therapeutically [21]. Thus there is no essential difference between type I and type II bipolar disorder [22], which is just another way of saying severe and moderate bipolar illness, just as there is no essential difference between mild and severe hypertension, or mild and severe diabetes, or mild and severe heart disease, or mild and severe ulcers. They are the same disease processes, just earlier or later in development, or milder versus more severe in nature.

So we see the unscientific logic that flows from the eclectic theory of DSM-III [4, 23], combined with the wishes of proponents of borderline personality. Completely different diagnoses—bipolar illness versus borderline personality—are seen as similar in nature, and the very same diagnosis—mania when severe versus mania when mild (hypomania)—is seen as two completely different entities.

These basic errors in scientific interpretation of diagnoses need to be corrected at the outset of any discussion of borderline personality versus bipolar illness. Once these conceptual mistakes are corrected, we can interpret the clinical and scientific literature more clearly, which we will do below.

Bipolar Disorder is Not Overdiagnosed

In one of the characteristic delusions that tend to characterize the sects of psychiatry, there is a widespread false belief that bipolar illness is overdiagnosed. It is not now; it never has been. Some borderline experts speak of "bipolar imperialism" [24].

As individuals from underdeveloped countries, it is ironic, if not offensive, to hear white North American males call others imperialist. It would be rather like those same persons calling others racist. They are the last people who should use such epithets. In fact, they should apologize for such usage.

But this tendentiously hostile language also points some of the clearly political, economic, and frankly territorial aspects of this debate. Perhaps some "experts" are concerned about their "territory" of prestige and income. If there has been any imperialism, the empirical literature proves that it was schizophrenic from 1920 to 1970 [25], then "major depressive" since then [26, 27], with borderline personality often "comorbidly" coming along for the ride. There has never been an empirical study that has ever shown that bipolar illness was more commonly diagnosed in those who did not have it than undiagnosed in those who had it. Bipolar illness, however defined, has never been overdiagnosed.

We will prove these points historically, then empirically.

Historically, when DSM-III was constructed, the broad Kraepelinian recurrent manic-depressive illness (MDI) concept was split up into episodic unipolar and bipolar psychoses [28], and then unipolar depression was broadened to include non-episodic melancholia and neurotic depressive conditions [6]. Major depressive disorder (MDD) is thus a very broad spectrum [29], much of which used to be part of MDI, while bipolar disorder is a very narrow definition [28], much smaller than prior MDI. Thus, it is *not* the case historically that DSM has encouraged the diagnosis of bipolar illness. In fact, the whole bipolar concept is but a rump of the original MDI concept; DSM-III is not Kraepelinian, it is Leonhardian in limiting the bipolar diagnosis severely [30]. DSM-IV was forced to broaden that rump bipolar diagnosis by acknowledging the existence of hypomanic episodes, defined for over a century, but since the broadening of bipolar illness is such a terrible offense, the leaders of DSM-IV explicitly admit that they tried to force clinicians not to diagnose bipolar disorder by not allowing antidepressant-induced mania as diagnostic and by narrowing the mixed definition [14]. Clinicians have disputed the indisputable fact that in some patients antidepressants increase suicidality [31] and cause actual deaths. Clinicians wonder why. They don't tend to realize that if we refuse to accept nature as it is, and call "depressed" what is mixed, or refuse to diagnose the bipolar spectrum in favor of borderline personality, and then give antidepressants that worsen suicidality in mixed states [32, 33], then patients will die. The antidepressants have gotten the blame; DSM-IV is equally liable.

Not only has bipolar disorder not been discouraged by DSM in the past three decades, mood stabilizers have not increased in usage, unlike what many believe. Extensive analysis of national US practice data shows that all drug classes increased in usage from the 1990s until two decades later, *except* mood stabilizers [34].

But what of those infamous data, purporting to prove bipolar overdiagnosis [35]. Of patients diagnosed clinically with bipolar illness by community practitioners in Rhode Island, about half did not meet bipolar type I or type II criteria using research diagnostic interviews. Hence bipolar illness is overdiagnosed. But if one looks at other diagnostic studies, like the Epidemiological Catchment Area (ECA) study [36] or even most recently the DSM-5 field trials [37], one finds similar rates of

about one half or more misdiagnosis for almost all psychiatric conditions, including in the ECA study (based on conversion of kappa values to percent disagreement rates): mania, 55 %; schizophrenia, 59 %; and MDD, 61 % [36]. One must then conclude that OCD and schizophrenia and MDD are all overdiagnosed because 40 % or more people diagnosed with them do not have those conditions either.

Similar results were found in the DSM-5 field trials. With a kappa value of 0.32 [37], MDD had a percent agreement of less than 50 %, just as in the Rhode Island study for bipolar disorder.

Can it be that every single psychiatric diagnosis is overdiagnosed? If so, then what is being underdiagnosed? And if it is the case that all are overdiagnosed, then why should we focus just on bipolar disorder? Why not emphasize the overdiagnosis of MDD and OCD and schizophrenia and even borderline personality?

In fact, it is logically incoherent to claim that most illnesses are overdiagnosed. These disagreement rates do not, by themselves, prove or disprove "over" diagnosis. They only demonstrate unreliability of diagnosis.

Clinicians diagnose things differently. If one starts by what clinicians diagnose, one will always find unreliability in real-world practice. This fact is proven by the ECA study and the DSM field trials; it is not unique to bipolar illness, and it does not prove overdiagnosis at all. Similar reliability rates of 50 % or less are found with asthma, chronic cholecystitis, celiac disease, and dementias [38]. One must suppose they are all stunningly overdiagnosed.

Instead, the claim of overdiagnosis entails something more than unreliability: if a diagnosis is overdiagnosed, it should be incorrectly diagnosed in those who do not have it more so than it incorrectly missed in those who have it. If a condition is underdiagnosed, the reverse would be the case. So we must begin by those who have the diagnosis, based on our gold standard: not what clinicians say using unclear methods (that's reliability), but what researchers claim using the gold standard interview methods. In the Rhode Island study, in those who had bipolar illness diagnosed by the researchers, 30 % were not diagnosed by clinicians [35]. In those who did not have bipolar illness using research interviews, only 13 % were diagnosed as having it erroneously by clinicians. The researchers proved a threefold underdiagnosis rate, not overdiagnosis, despite their own claim to the contrary, presumably because they refuse to believe their own data [38].

Prior studies by our group agree with the correct interpretation of the Rhode Island data, demonstrating repeatedly about 40 % underdiagnosis of bipolar disorder [26, 27]. We have also repeated the Rhode Island analysis in the International Mood Network in a dozen countries, and we found that 29 % of patients with BD are underdiagnosed as having MDD, but only 8 % of MDD patients suffer from the disease of bipolar overdiagnosis [39]. Others have found this evidence too: in a German study in 185 psychologists given case vignettes [40], only about 40 % of bipolar cases were correctly diagnosed, the majority being mislabeled MDD, while *zero* of MDD cases were diagnosed with bipolar illness.

The Bipolar Spectrum Is Not About Mood Lability or Impulsivity

We can now turn to the question of how this underdiagnosed disease compares to the psychological construct of borderline personality. There has been much debate about the question of overlap, especially with broadened bipolar spectrum definitions, which, we may note, are not new, but are still narrower than the classic broad original Kraepelinian concept of MDI (contrary to the false interpretations of some psychiatric historians [41]). To examine the validity of any diagnostic definition, there is consensus on the use of the classic concept of validators of diagnosis: phenomenology, course of illness, genetics, biology, and treatment effects [42] (Table 6.1).

Using such validators, a strong empirical case can be made for validity of the claim that bipolar illness is a spectrum, not an all-or-nothing condition definable as the presence or absence of mania (or even hypomania) [43].

This claim is best understood by recognizing that mania or manic symptoms are not definable centrally by mood or even mood lability. Nor are manic symptoms centrally describable through symptoms of impulsivity. Certainly, manic presentations often involve mood lability and impulsivity, but those symptoms are nonspecific, occurring in many other conditions. Instead, there is good evidence that the most common specific feature of manic phenomenology, what differentiates it most from depression or other conditions, is psychomotor activation [44, 45], not euphoric mood or mood lability or impulsivity per se.

Instead of those nonspecific symptoms, spectrum concepts focus on the course of the illness as central to diagnosis, meaning recurrence, and a biology that differs from pure depression, as expressed in poor antidepressant response [43]. These spectrum concepts pay attention to manic symptoms as being relevant, not ignoring them unless they are part of full manic episodes [46]. And the emphasis is on the fact that core of mania is psychomotor activation [44, 45]—meaning rapidity of thought and feelings and activities—not mood states of a certain kind or specific behaviors (like euphoria and sexual impulsivity, which occur in a minority of even full-blown manic episodes [28]).

Table 6.1 Diagnostic validators that distinguish bipolar illness and borderline personality

Diagnostic validator	Borderline personality	Bipolar illness
Symptoms	Dissociative symptoms	Euphoric mood
	Recurrent parasuicidal self-mutilating behavior	Increased goal-directed activity
		Psychomotor activation
Genetics	Nonspecific	Very strong heritability
Biology	Nonspecific	Amygdala enlargement
		Hippocampal atrophy
Course	High prevalence of sexual abuse	Very severe recurrent mood episodes (excluding mood temperaments)
Treatment	Complete cure with psychotherapies in 1/3 or more	Complete cure with mood stabilizers in 1/3 or more

In the original concept of MDI, the emphasis was on a recurrent course, not polarity [47], and on genetics [47], and later evidence has greatly strengthened the genetic specificity of this condition [48] and provided support for a high diagnostic specificity to antidepressant-induced mania [49–51]. In previous work on the bipolar spectrum concept [43], emphasizing course of illness features in severe recurrent depression, the differential diagnosis mainly had to do with unipolar depression. All bipolar spectrum patients were seen as having severe depression; the only question was whether they should be seen as unipolar or bipolar. This approach to the spectrum concept does not tie into the differential diagnosis with personality disorder as much as the spectrum concepts of Akiskal, who sees the spectrum as trailing into mood temperaments [52].

Mood Temperaments and Personality

The concept of mood temperaments is perhaps the key issue of distinction in relation to personality "disorders." It is another common misconception among psychoanalytically oriented clinicians to think about personality only in terms of personality "disorders." It is perhaps an irrefutable scientific fact that there are orders of magnitude more scientific data for validity of personality *traits* than for DSM-defined personality disorder [53]. Despite this clear scientific evidence, the DSM-5 process ended with a refusal to allow personality traits into the psychiatric diagnostic system, whereas the prior, poorly scientifically validated, structure of personality disorder was retained with minor alterations.

It is scientifically more sound to recognize, however, that one first can address personality with the concept of personality traits, among which a number are replicated with sometimes varying designations for the same type of trait: neuroticism (anxiety, harm avoidance), extroversion (sociability, other-centeredness), and openness to experience (risk taking, sensation seeking, curiosity, reward dependence), among others [53].

The concept of mood temperaments can be related to personality traits, the idea being that there is a biology to personality [54], even though there are also important obvious environmental and psychosocial components. Ever since Kraepelin [47], and then Kretschmer [55], almost a century ago, mild personality variants of mood illnesses have been described, using various terms for the same types: dysthymia (constitutional depression), hyperthymia (constitutional excitement), and cyclothymia (a combination of both). Recent genetic [56], biological [57], and clinical [58–60] studies indicate linkages between these mood temperaments and mood illnesses (unipolar depression and bipolar illness).

Thus, temperaments can be seen as dimensional extremes of normal personality traits which are biologically and genetically related to mood illnesses, being basically mild *formes fruste* of mood illnesses. In contrast, personality "disorders" are categorical constructs based mostly on psychoanalytic concepts, with little genetic

basis [48] and limited biological knowledge about their etiologies or mechanisms [61]. If temperament concepts are valid, then the tendency to ignore them (hyperthymia is not even included in DSM revisions) would lead to an overdiagnosis of borderline personality.

It is worth emphasizing: temperament concepts are twice as old—about a hundred years—than the borderline concept, have stronger genetic and biological bases, and require no psychoanalytic ideological commitments.

Mixed Mood States and Borderline Personality

Another area of spectrum overlap has to do with the concept of mixed states [45]: these agitated excited depressive states can easily be misdiagnosed as "MDD" with borderline personality, if one focuses on the irritability and impulsivity that are associated with them.

Mixed mood states are very important phenomenologically if it is true, as many studies indicate, that they are the most common type of mood episode [45, 62]. Kraepelin refused to base his nosology on polarity, presence or absence of depression versus mania, unlike DSM-III onwards, partly because he observed that most mood episodes in manic-depressive illness did not belong purely to one pole or the other [47, 63]. Most mood episodes were mixed, with perhaps the most common type of mixed mood episode being what is sometimes called agitated depression or more recently "mixed depression": severe depression with psychomotor excitation, which involves marked mood reactivity, irritability, and usually psychomotor agitation [45]. Sometimes frank manic symptoms like brief periods of hyperactivity with flight of ideas and even heightened sexual drive and impulsivity occur. This mixed depression is completely ignored by the DSM nosology and labeled "major depression" as if all of these manic symptoms can be dismissed as nonexistent unless they happen for 4–7 days or longer [62]. Ignoring this unscientific, arbitrary DSM definition, recent data show that about one-half of all depressive episodes, whether occurring in bipolar disorder or not, are accompanied by multiple manic symptoms [64], as in the mixed depression description above.

Since DSM ignores the reality of these mixed mood episodes, it is likely that such patients often get mistakenly diagnosed with two conditions they do not have—MDD comorbid with borderline personality—rather than the one illness they do have: mixed depression (part of manic-depressive illness).

The Solution

Given all of these diagnostic problems, how is one to differentiate a patient with borderline personality from a patient with bipolar illness, mood temperaments, or mixed depressive episodes?

We propose a simple solution, based on our prior work on the mistaken claim of bipolar overdiagnosis [65]:

> Use non-symptom diagnostic validators to increase positive predictive value before applying DSM-style symptom definitions for mania or borderline personality.

All want to avoid false-positives. One could always avoid false-positives for low prevalence conditions (<20 % would be considered low prevalence, for statistical purposes), like bipolar illness, by just never diagnosing them. If bipolar illness happens in at most 5 % of the population, then if we never diagnose it, we would be right 95 % of the time. Many bipolar skeptics do just this: they have rarely seen a bipolar illness they did not refuse to diagnose. And they would be correct most of the time, statistically. But we presume we actually want to diagnose and help those suffering from this highly treatable and deadly illness.

So how can we avoid false positives while also diagnosing uncommon conditions frequently enough?

The DSM approach, loudly proclaimed by the leader of its 4th revision [15], is to attack any effort to broaden diagnostic definitions: spectrum concepts are rejected tout court and even seen as slightly evil. By making diagnoses narrow, we increase specificity to reduce false-positives. Hypomania can never be allowed to be defined as less than 4 days, even though there is zero evidence for that cutoff, and there is notable evidence for lower durations as meeting nosological validity requirements [22].

The problem with this approach, despite its use for three decades and counting, is that it can clearly be shown to be statistically doomed [65]. Predictive value is sensitive to prevalence. So with a low prevalence condition, like almost any psychiatric illness, if all we do is apply DSM criteria as our diagnostic test, we will always have a high rate of false-positives until we reach very high specificities of greater than 95 %, which is only attained with very sensitive laboratory tests in medicine, not with variable clinical judgments. To achieve a PPV of even 50 %, the rate that has been consistently misinterpreted in the Rhode Island study as representing overdiagnosis, we would need a diagnostic specificity for DSM criteria of 90 %, which is hardly attained with much more careful instruments like echocardiograms and x-rays. Clinical diagnostic reliability rarely reaches 80–90 % even in highly structured settings like research studies, much less clinical practice where it tends to be 50–70 % or lower [38, 65].

In other words, the low prevalence of a condition dooms any DSM-like effort to reduce false-positives by being *diagnostically puritanical.*

There is only one solution: to increase the prevalence. Of course we can't go out into the community and infect people with bipolar illness, so how can we increase the prevalence?

We increase it by only allowing people into our clinical theater of evaluation who are already more likely to have bipolar illness [65]. We screen for clinical risk factors for bipolar illness other than the DSM criteria (i.e., mania): genetics, course, and treatment effects. Thus, if someone has bipolar genetics and early-onset depression before age 25 years, they already have a 50 % prior probability of meeting DSM-defined bipolar disorder criteria [65]. Then when we apply those

criteria to that person, we will have 80 % positive and negative predictive values [65], much better than standard clinical practice and much better than even DSM-148 will ever be.

Now we can use this idea for the bipolar-borderline debate and see how available evidence applies.

Diagnostic Validators

Beginning with phenomenology, we found that manic mood symptoms differentiated bipolar illness from borderline personality. In one study by our group [66] in 260 patients with mood illnesses (68 % females), bipolar illness could be distinguished from borderline personality disorder, using DSM-IV definitions, based on a triad of euphoric mood (odds ratio, OR = 4.02, 95 % confidence intervals, CI:1.80, 9.15), mood episodicity (OR = 3.48; CI: 1.49–8.39), and increased goal-directed activities (OR = 3.9; CI: 1.73–8.96), whereas borderline personality disorder was not predicted by any mood symptoms examined. The only clinical feature predictive of borderline personality, as opposed to bipolar illness, was female gender (OR = 3.41; CI: 1.29–13.70).

In the BRIDGE study [67], which assessed an unselected mood population with depressive episodes, mixed depression as described above was assessed. Even using that very broad definition of mixed depression, borderline personality was able to be distinguished from mixed depression based on four of its DSM-IV features: fears of abandonment, identity disturbance, recurrent suicidal or self-mutilating behavior, and dissociative symptoms. The ability to distinguish these borderline features is all the more impressive when one appreciates that this is a sample of patients with clinical depression in which the prior probability of bipolar illness, simply based on presence of depression and the clinical/demographic features of the sample, is about 50 % [65].

Another key differentiating feature of phenomenology is parasuicidal self-harm in borderline personality [68]. A recent literature review of 51 articles [69] found that self-mutilation is common in borderline personality (50–80 % of cases) and is frequently repetitive (41 % of patients have more than 50 self-mutilation acts). In contrast, parasuicidal behavior is much less common in bipolar illness. In the National Comorbidity Survey ($n = 5{,}877$) the prevalence of self-harm among patients with type I bipolar illness was only 0.9 %. In other words, the difference between type I bipolar illness and borderline personality is about a 50–80-fold increased relative risk of parasuicidal self-harm in borderline personality. This is five- to eightfold higher than the association between tobacco and lung cancer [70]. A more definitive specific distinguishing feature between two clinical syndromes can hardly be found. The importance of the NCS data is that they are epidemiological, not clinical. They are based on determining prevalence of parasuicidal behavior in persons with bipolar illness who are in the community, not those who seek treatment in clinicians' offices. By using clinically selected samples, higher rates of parasuicidal

behavior are seen, even in bipolar type I illness, in some studies, but these samples involve a selection bias of those who seek help and do not generalize to the entire bipolar population. In contrast, the NCS study does generalize to the whole bipolar population and is probably the most valid data on which to base judgments about sexual trauma prevalence. Even with this limitation, the highest parasuicidal behavior rate reported in clinical studies is 36 %, which remains twofold less frequent than in borderline personality [71].

A critic could claim that matters are different for type II bipolar illness, as opposed to type I, despite the fact, as we've discussed above, that the assumption that there are major differences between type I and type II bipolar illness is not based on a solid scientific evidence base. Nonetheless, the parasuicidal behavior rate in type II bipolar illness has not been studied empirically, in our review of the literature. In contrast, suicide attempt and suicide rates have been demonstrated to be very similar between type I and type II bipolar illness [72].

Turning to the nosological validator of genetics, bipolar illness is one of the two most heritable mental illnesses, along with schizophrenia, both having about 80 % heritability, similar to Alzheimer's dementia [48]. This rate is about twice as much as borderline personality or other personality traits or disorders, which tend to have about 40–50 % heritability [48, 73], a relatively low rate indicating that environmental aspects of etiology are as important as genes for borderline personality. In contrast, bipolar illness is almost completely genetic, similar to the heritability of height [73].

On the validator of course of illness, episodicity versus chronicity may not be definitive in differentiating bipolar illness from borderline personality if we include the concept of mood temperaments, which are by nature constant personality states. However, a key course feature that seems to differentiate these conditions is a history of sexual abuse. In a commonly cited meta-analysis of 21 studies, 50–76 % of patients with borderline personality disorder had experienced sexual trauma. Many have downplayed these results by claiming that the average effect size for the association between childhood sexual abuse and borderline personality is only moderate ($r = 0.279$) [74]. This attempt to downplay the high rate of sexual abuse in borderline personality, by focusing on the correlation coefficient, obfuscates a key distinction with bipolar illness, where sexual abuse occurs in less than 30 % of bipolar subjects [75, 76]. A recent systematic review including 3,407 bipolar patients found a 24 % prevalence of sexual trauma in bipolar illness [75], which is only slightly higher than the general population (13–17 % in women and 2.5–5 % in men: thus 15–22 % overall). The key finding is that sexual abuse is at least two times more common in borderline personality than in bipolar illness, and rates in bipolar illness are almost the same as the general population.

Regarding biological validators, bipolar illness is associated with enlargement of the amygdala and hippocampal atrophy, which is correlated with a number of mood episodes [77]. Borderline personality is not. Other biological changes found in borderline personality, such as deficits in integration between cognition and emotional processing stimuli [78], are not unique to borderline personality but are also found in other neuropsychiatric syndromes, including schizophrenia and bipolar illness [79].

On the final validator of treatment, about one-third of patients with bipolar illness are completely cured with mood stabilizers like lithium [28]. Patients with borderline personality have at best modest symptomatic improvement with mood stabilizers or neuroleptics and are not generally cured with medications [80]. In contrast, a substantial minority of patients with borderline personality appear to approve with psychotherapies, with complete remission in about one-third or more [81, 82], while bipolar illness never fully remits with psychotherapies alone [28].

In sum, bipolar illness can be differentiated from borderline personality with important diagnostic validators, as summarized in Table 6.1. It is irrelevant that many of these common predictors of these conditions, like sexual abuse and bipolar genetics and recurrent course, are not part of DSM criteria; they should be. Psychiatric diagnosis limited to DSM criteria is unscientific and poor psychiatric practice [30]. These other non-DSM predictors are important variables to increase the PPV of these conditions, thereby reducing false-positives in either direction.

Case Vignettes

Now we can apply these ideas to three case vignettes: one where the patient is hyperthymic not borderline, another borderline not bipolar, and a third bipolar only not bipolar plus borderline.

Case 6.1 Hyperthymia, Not Borderline

A 25-year-old adopted Asian female is treated with bupropion 300 mg/day and atomoxetine 60 mg/day. She reports chronic and constant suicidal ideation for the past 10 years. She has abused alcohol and marijuana regularly for 10 years and cocaine for the past 2 years. She was hospitalized once at age 14 and has had many overdoses and some cutting behavior. She also has bulimia at times. She was adopted, so her biological family information is not available. She grew up in a wealthy, white, upper-class Boston suburb, having been adopted by a very well-to-do family. Her mother accompanied her, and the family appears very supportive of her. She went to excellent schools and never experienced any trauma of any kind. She was never married, has no children, graduated college, and lives alone while working for a retail store.

She describes past manic symptoms as "I'm always rushing around, racing thoughts, pretty hyper, I can get so much shit done"; this is associated with talkativeness and distractibility: "I'm always confident." She has impulsive behavior of all kinds: sexual, spending, and reckless driving. "I've always been nocturnal, I like to stay up at night." Normally, she sleeps at 4 a.m. and wakes up at 8, without being tired. When she is depressed, she has very low energy and sleeps over 13 h nightly. There are no definable episodes of mania above her hyperthymic baseline.

She was diagnosed with borderline personality disorder plus MDD at age 15 and has received weekly psychotherapy for 10 years; she also has taken antidepressants for the past 5 years. She briefly received lithium at age 15, added to citalopram, without benefit.

Her course of illness is rapid cycling: 3 months ago, she had depression for 1 month, followed by her hyperthymic baseline for 2 months before evaluation.

After evaluation, antidepressants were discontinued, and her chronic suicidal ideation, persistent for 10 years, completely resolved immediately. In a 6-month follow-up, she refused mood stabilizer treatment, but was much better off antidepressants without psychotherapy than she had been previously.

Case 6.2 Borderline, Not Bipolar

A 19-year-old college student female seeks evaluation for possible medication treatment. She describes early childhood sexual trauma around age 4 by her father, with some persistence to age 8. She is not taking and has never taken any medications and has had no hospitalizations and no suicide attempts. Her family history consists of depression in a cousin, but no bipolar illness or suicides or other major mental illness. She has frequent sexual nightmares related to her father and describes severe depression beginning at age 9 and SI beginning at age 14. She experienced skin tearing as a child beginning at age 5. She has burned herself multiple times in the past 2 years and cut herself a few months ago. "I enjoy the feeling of burning on my skin." She lights herself on fire by lighting a fabric and taping it to her skin. Her mood is labile on a daily basis but with no psychomotor activation as with manic symptoms: "I reach a very low point at some point each day, and then I'll enter into a state of numbness, where I feel nothing at all, happy or sad. Sometimes I don't even feel anything physically at all." She has some anorexia: "Part of me enjoys the feeling of starvation." She gets angry easily: "I easily get into rages and then I'll yell at a bunch of friends, then I'll clean to calm myself down, and then I'll start crying and call them all up to apologize." She describes no periods of psychomotor activation lasting even 1 day or more, and her baseline temperament appears high in neuroticism and average in extraversion and openness to experience, without any evidence of decreased need for sleep or other hyperthymic features. Medications were not recommended; long-term psychotherapy was.

Case 6.3 Bipolar, Not Bipolar and Borderline

A 23-year-old female graduate student initially came for treatment taking oxcarbazepine 750 mg/day and fluoxetine 1.6 mg/day. She had an allergy to lamotrigine (swollen throat), past substance abuse with opiates and benzodiazepines, current excessive alcohol use, three psychiatric hospitalizations, and one overdose.

She described childhood sexual abuse and also the trauma of a boyfriend committing suicide. She had flashbacks and nightmares to both traumas. Her relationship with her family was ambivalent, supportive from another city but not directly involved in her care. Her manic symptoms were "no need to sleep, talking a lot, I'd get impulsive, mostly be cutting myself or by drinking more, racing thoughts, irritability, and increased sexual activity." "My suicide attempts are when I'm manic." Duration of manic symptoms were 1 week or longer. One month before the initial evaluation, she had 2 days of manic symptoms followed by 3 weeks of depression. Depression and mania began at age 14, with many episodes, and duration of typical depressive episode being 1 month; she was diagnosed bipolar at age 19. There were no past psychotic symptoms. Depressive episodes were mixed: associated with marked psychomotor agitation, psychic tension, talkativeness, frequent weeping, racing thoughts, marked irritability, and insomnia. She had failed to respond to multiple antidepressants. She had antidepressant-induced mania with escitalopram. Neuroleptics helped manic symptoms but had side effects of weight gain or akathisia that made them intolerable.

In sum, years of psychotherapy and multiple antidepressants/neuroleptics were ineffective.

In a prospective 2-year treatment, her clinician observed that she was very aware of her symptoms, quite compliant with medications and with alcohol abstinence, and able to identify and express her symptoms and her needs accurately and effectively. She also had a certain feeling about her that other psychiatrists might have interpreted as caginess or manipulativeness. On one occasion, when he was trying to get her to take a certain treatment regimen, she said to her clinician, "Dr. Ghaemi, you can be very manipulative."

In prospective treatment, she had trouble with akathisia or inefficacy with multiple neuroleptics, no benefit with lithium + carbamazepine, and was hospitalized once again with serious suicidal ideation. We eventually reached a regimen of lithium 1,200 mg/day, lamotrigine 200 mg/day, iloperidone 3 mg/day, and propranolol ER 120 mg/day, which led to complete recovery with over 1 year of no mood symptoms at all and no further PTSD symptoms and marked improvement in function and complete resolution of suicidality, all in the absence of any intensive psychotherapy oriented at purported borderline or PTSD features.

Conclusions

Major sexual trauma that derails personality development in early childhood has important consequences and can produce a clinical picture of complex PTSD symptoms that we call borderline personality. This is a truth, but it is a falsehood if this picture is allowed to deny and ignore our most treatable common psychiatric disease: bipolar illness. Irrationally held truths are more harmful than reasoned errors [83].

References

1. Paris J, Gunderson J, Weinberg I. The interface between borderline personality disorder and bipolar spectrum disorders. Compr Psychiatry. 2007;48(2):145–54.
2. Akiskal HS. Demystifying borderline personality: critique of the concept and unorthodox reflections on its natural kinship with the bipolar spectrum. Acta Psychiatr Scand. 2004;110(6): 401–7.
3. Paris J. Borderline or bipolar? Distinguishing borderline personality disorder from bipolar spectrum disorders. Harv Rev Psychiatry. 2004;12(3):140–5.
4. Ghaemi S. The rise and fall of the biopsychosocial model: reconciling art and science in psychiatry. Baltimore: Johns Hopkins University Press; 2009.
5. Spitzer RL, Endicott J, Robins E. Research diagnostic criteria: rationale and reliability. Arch Gen Psychiatry. 1978;35:773.
6. Shorter E. Before Prozac: the troubled history of mood disorders in psychiatry. New York: Oxford University Press; 2009.
7. Decker HS. The making of DSM-III®: a diagnostic manual's conquest of American Psychiatry. New York: Oxford University Press; 2013.
8. Goldstein S. Console and classify: the French psychiatric profession in the 19th century. Chicago: University of Chicago Press; 2002.
9. Angst J, Marneros A. Bipolarity from ancient to modern times: conception, birth and rebirth. J Affect Disord. 2001;67(1–3):3–19.
10. Kernberg O. Borderline personality organization. J Am Psychoanal Assoc. 1967;15(3): 641–85.
11. Boestrom A. Zustandbild und Krankheit in der psychiatrie. Klinische Wochenshcrift. 1923;2: 1728–31.
12. Gunderson J. Borderline personality disorder. Washington, DC: American Psychiatric Press; 1984.
13. Wakefield JC. The concept of mental disorder: diagnostic implications of the harmful dysfunction analysis. World Psychiatry. 2007;6(3):149–56.
14. Frances A. DSM in philosophyland: curioser and curioser. http://alien.dowling.edu/~cperring/aapp/bulletin.htm. 2010. Cited 8 Nov 2010; Available from: http://alien.dowling.edu/~cperring/aapp/bulletin.htm.
15. Frances A. A warning sign on the road to DSM-V: beware of its unintended consequences. Psychiatr Times. 2009;26(8):1–4.
16. Simpson SG, Folstein SE, Meyers DA, McMahon FJ, Brusco DM, DePaulo Jr JR. Bipolar II: the most common bipolar phenotype? Am J Psychiatry. 1993;150(6):901–3.
17. Sobczak S, Honig A, Nicolson NA, Riedel WJ. Effects of acute tryptophan depletion on mood and cortisol release in first-degree relatives of type I and type II bipolar patients and healthy matched controls. Neuropsychopharmacology. 2002;27(5):834–42.
18. Sobczak S, Riedel WJ, Booij I, Aan Het Rot M, Deutz NE, Honig A. Cognition following acute tryptophan depletion: difference between first-degree relatives of bipolar disorder patients and matched healthy control volunteers. Psychol Med. 2002;32(3):503–15.
19. Dickerson FB, Boronow JJ, Stallings C, Origoni AE, Cole S, Leister F, et al. The catechol O-methyltransferase Val158Met polymorphism and herpes simplex virus type 1 infection are risk factors for cognitive impairment in bipolar disorder: additive gene-environmental effects in a complex human psychiatric disorder. Bipolar Disord. 2006;8(2):124–32.
20. Soderlund J, Olsson SK, Samuelsson M, Walther-Jallow L, Johansson C, Erhardt S, et al. Elevation of cerebrospinal fluid interleukin-1ss in bipolar disorder. J Psychiatry Neurosci. 2011;36(2):114–8.
21. Tondo L, Baldessarini R, Hennen J, Floris G. Lithium maintenance treatment: depression and mania in bipolar I and II disorders. Am J Psychiatry. 1998;155:638–45.
22. Berk M, Dodd S. Bipolar II disorder: a review. Bipolar Disord. 2005;7(1):11–21.

23. Ghaemi S. Taking disease serious: against "pragmatic" nosology. In: Kendler KS, Parnas J, editors. Philosophical issues in psychiatry II: Nosology. Oxford: Oxford University Press; 2012. p. 42–52.
24. Paris J. The bipolar spectrum: a critical perspective. Harv Rev Psychiatry. 2009;17(3):206–13.
25. Cooper JE, Kendell RE, Gurland BJ, Sartorius N, Farkas T. Psychiatric diagnosis in New York and London. Oxford: Oxford University Press; 1972.
26. Ghaemi SN, Boiman EE, Goodwin FK. Diagnosing bipolar disorder and the effect of antidepressants: a naturalistic study. J Clin Psychiatry. 2000;61(10):804–8, quiz 9.
27. Ghaemi SN, Sachs GS, Chiou AM, Pandurangi AK, Goodwin FK. Is bipolar disorder still underdiagnosed? Are antidepressants overutilized? J Affect Disord. 1999;52:135–44.
28. Goodwin F, Jamison K. Manic depressive illness. 2nd ed. New York: Oxford University Press; 2007.
29. Ghaemi SN, Vohringer PA, Vergne DE. The varieties of depressive experience: diagnosing mood disorders. Psychiatr Clin North Am. 2012;35(1):73–86.
30. Ghaemi S. On depression: diagnosis, drugs, and despair in the modern world. Baltimore: Johns Hopkins University Press; 2013.
31. Hammad TA, Laughren T, Racoosin J. Suicidality in pediatric patients treated with antidepressant drugs. Arch Gen Psychiatry. 2006;63(3):332–9.
32. Dilsaver SC, Chen YW, Swann AC, Shoaib AM, Krajewski KJ. Suicidality in patients with pure and depressive mania. Am J Psychiatry. 1994;151(9):1312–5.
33. Berk M, Dodd S. Are treatment emergent suicidality and decreased response to antidepressants in younger patients due to bipolar disorder being misdiagnosed as unipolar depression? Med Hypotheses. 2005;65(1):39–43.
34. Mojtabai R, Olfson M. National trends in psychotropic medication polypharmacy in office-based psychiatry. Arch Gen Psychiatry. 2010;67(1):26–36.
35. Zimmerman M, Ruggero CJ, Chelminski I, Young D. Is bipolar disorder overdiagnosed? J Clin Psychiatry. 2008;69(6):935–40.
36. Anthony JC, Folstein M, Romanoski AJ. Comparison of lay DIS and a standardized psychiatric diagnosis. Arch Gen Psychiatry. 1985;42:667–75.
37. Regier DA, Narrow WE, Clarke DE, Kraemer HC, Kuramoto SJ, Kuhl EA, et al. DSM-5 field trials in the United States and Canada, Part II: test-retest reliability of selected categorical diagnoses. Am J Psychiatry. 2013;170(1):59–70.
38. Smith D, Ghaemi S. Is underdiagnosis the main pitfall when diagnosing bipolar disorder? Yes. BMJ. 2010;340:c854.
39. Holtzman NS, Vohringer PA, Sullivan M, Lovdahl H, Correa E, Patkar A, et al., editors. Underdiagnosis of bipolar disorder: an international reality (abstract). In: American Psychiatric Association annual meeting, Philadelphia, 2012.
40. Bruchmuller K, Meyer TD. Diagnostically irrelevant information can affect the likelihood of a diagnosis of bipolar disorder. J Affect Disord. 2009;116(1–2):148–51.
41. Healy D. Mania: a short history of bipolar disorder. Baltimore: Johns Hopkins University Press; 2008.
42. Robins E, Guze SB. Establishment of diagnostic validity in psychiatric illness: its application to schizophrenia. Am J Psychiatry. 1970;126:983–7.
43. Ghaemi SN, Ko JY, Goodwin FK. "Cade's disease" and beyond: misdiagnosis, antidepressant use, and a proposed definition for bipolar spectrum disorder. Can J Psychiatry. 2002;47(2):125–34.
44. Cassano GB, Rucci P, Benvenuti A, Miniati M, Calugi S, Maggi L, et al. The role of psychomotor activation in discriminating unipolar from bipolar disorders: a classification-tree analysis. J Clin Psychiatry. 2012;73(1):22–8.
45. Koukopoulos A, Sani G, Koukopoulos AE, Manfredi G, Pacchiarotti I, Girardi P. Melancholia agitata and mixed depression. Acta Psychiatr Scand Suppl. 2007;433:50–7.
46. Angst J, Gamma A, Bowden CL, Azorin JM, Perugi G, Vieta E, et al. Diagnostic criteria for bipolarity based on an international sample of 5,635 patients with DSM-IV major depressive episodes. Eur Arch Psychiatry Clin Neurosci. 2012;262:3–11.

47. Kraepelin E. Manic-depressive insanity and paranoia. Edinburgh: E & S Livingstone; 1921.
48. Bienvenu OJ, Davydow DS, Kendler KS. Psychiatric 'diseases' versus behavioral disorders and degree of genetic influence. Psychol Med. 2011;41(1):33–40.
49. Perlis RH, Uher R, Ostacher M, Goldberg JF, Trivedi MH, Rush AJ, et al. Association between bipolar spectrum features and treatment outcomes in outpatients with major depressive disorder. Arch Gen Psychiatry. 2011;68:351–60.
50. Tondo L, Vazquez G, Baldessarini RJ. Mania associated with antidepressant treatment: comprehensive meta-analytic review. Acta Psychiatr Scand. 2010;121(6):404–14.
51. Tondo L, Baldessarini RJ, Vazquez G, Lepri B, Visioli C. Clinical responses to antidepressants among 1036 acutely depressed patients with bipolar or unipolar major affective disorders. Acta Psychiatr Scand. 2013;127(5):355–64.
52. Akiskal HS, Pinto O. The evolving bipolar spectrum. Prototypes I, II, III, and IV. Psychiatr Clin North Am. 1999;22(3):517–34, vii.
53. Matthews G, Deary I, Whiteman M. Personality traits. 3rd ed. Cambridge: Cambridge University Press; 2009.
54. Eysenck H. The scientific study of personality. London: Routledge Kegan and Paul; 1952.
55. Kretschmer E. Physique and character. New York: Cooper Square Publishers; 1921 (1970).
56. Kelsoe JR. The genetics of bipolar disorder. Psychiatr Ann. 1997;27:285–92.
57. Serretti A, Mandelli L, Lorenzi C, Landoni S, Calati R, Insacco C, et al. Temperament and character in mood disorders: influence of DRD4, SERTPR, TPH and MAO-A polymorphisms. Neuropsychobiology. 2006;53(1):9–16.
58. Vöhringer P, Whitham E, Thommi S, Holtzman N, Khrad H, Ghaemi S. Affective temperaments and clinical practice: a validation study in mood disorders. J Affect Disord. 2012;136(3): 577–80.
59. Hantouche EG, Akiskal HS. Toward a definition of a cyclothymic behavioral endophenotype: which traits tap the familial diathesis for bipolar II disorder? J Affect Disord. 2006;96(3): 233–7.
60. Akiskal H. Temperament and mood disorders. Harv Ment Health Lett. 2000;16(8):5–6.
61. Widiger TA, Simonsen E, Krueger R, Livesley WJ, Verheul R. Personality disorder research agenda for the DSM-V. J Pers Disord. 2005;19(3):315–38.
62. Koukopoulos A, Sani G. DSM-5 criteria for depression with mixed features: a farewell to mixed depression. Acta Psychiatr Scand. 2014;129(1):4–16.
63. Salvatore P, Baldessarini RJ, Centorrino F, Egli S, Albert M, Gerhard A, et al. Weygandt's On the Mixed States of Manic-Depressive Insanity: a translation and commentary on its significance in the evolution of the concept of bipolar disorder. Harv Rev Psychiatry. 2002;10(5): 255–75.
64. Angst J, Azorin JM, Bowden CL, Perugi G, Vieta E, Gamma A, et al. Prevalence and characteristics of undiagnosed bipolar disorders in patients with a major depressive episode: the BRIDGE study. Arch Gen Psychiatry. 2011;68(8):791–8.
65. Phelps J, Ghaemi SN. The mistaken claim of bipolar 'overdiagnosis': solving the false positives problem for DSM-5/ICD-11. Acta Psychiatr Scand. 2012;126(6):395–401.
66. Vöhringer P, Alvear K, Medina S, Espinosa C, Alexandrovic K, Ruimallo P, et al. Differentiating Borderline Personality Disorder from Bipolar Disorder. (abstract) American Psychiatric Association annual meeting, May 5–9 2012, Philadelphia PA.
67. Perugi G, Angst J, Azorin JM, Bowden C, Vieta E, Young AH. The bipolar-borderline personality disorders connection in major depressive patients. Acta Psychiatr Scand. 2013;128: 376–83.
68. Brodsky BS, Cloitre M, Dulit RA. Relationship of dissociation to self-mutilation and childhood abuse in borderline personality disorder. Am J Psychiatry. 1995;152(12):1788–92.
69. Oumaya M, Friedman S, Pham A, Abou Abdallah T, Guelfi JD, Rouillon F. Borderline personality disorder, self-mutilation and suicide: literature review. Encéphale. 2008;34(5):452–8. Personnalite borderline, automutilations et suicide : revue de la litterature.
70. Boffetta P, Pershagen G, Jockel KH, Forastiere F, Gaborieau V, Heinrich J, et al. Cigar and pipe smoking and lung cancer risk: a multicenter study from Europe. J Natl Cancer Inst.

1999;91(8):697–701.
71. Joyce PR, Light KJ, Rowe SL, Cloninger CR, Kennedy MA. Self-mutilation and suicide attempts: relationships to bipolar disorder, borderline personality disorder, temperament and character. Aust N Z J Psychiatry. 2010;44(3):250–7.
72. Valtonen H, Suominen K, Mantere O, Leppamaki S, Arvilommi P, Isometsa ET. Suicidal ideation and attempts in bipolar I and II disorders. J Clin Psychiatry. 2005;66(11):1456–62.
73. Kendler KS, Prescott C. Genes, environment, and psychopathology. New York: Guilford Press; 2006.
74. Fossati A, Madeddu F, Maffei C. Borderline Personality Disorder and childhood sexual abuse: a meta-analytic study. J Pers Disord. 1999;13(3):268–80.
75. Maniglio R. Prevalence of child sexual abuse among adults and youths with bipolar disorder: a systematic review. Clin Psychol Rev. 2013;33(4):561–73.
76. Conus P, Cotton S, Schimmelmann BG, Berk M, Daglas R, McGorry PD, et al. Pretreatment and outcome correlates of past sexual and physical trauma in 118 bipolar I disorder patients with a first episode of psychotic mania. Bipolar Disord. 2010;12(3):244–52.
77. Strakowski SM, Delbello MP, Adler CM. The functional neuroanatomy of bipolar disorder: a review of neuroimaging findings. Mol Psychiatry. 2005;10(1):105–16.
78. Shamay-Tsoory SG, Tomer R, Berger BD, Aharon-Peretz J. Characterization of empathy deficits following prefrontal brain damage: the role of the right ventromedial prefrontal cortex. J Cogn Neurosci. 2003;15(3):324–37.
79. Ongur D, Lundy M, Greenhouse I, Shinn AK, Menon V, Cohen BM, et al. Default mode network abnormalities in bipolar disorder and schizophrenia. Psychiatry Res. 2010;183(1):59–68.
80. Soloff PH. Psychopharmacology of borderline personality disorder. Psychiatr Clin North Am. 2000;23(1):169–92, ix.
81. Lieb K, Zanarini MC, Schmahl C, Linehan MM, Bohus M. Borderline personality disorder. Lancet. 2004;364(9432):453–61.
82. Giesen-Bloo J, van Dyck R, Spinhoven P, van Tilburg W, Dirksen C, van Asselt T, et al. Outpatient psychotherapy for borderline personality disorder: randomized trial of schema-focused therapy vs transference-focused psychotherapy. Arch Gen Psychiatry. 2006;63(6):649–58.
83. Huxley TH. Aphorisms and reflections. London: Macmillan and Co.; 1907.

Part III
Modeling Mood and Personality: Dimensional and Categorical Formulation

Chapter 7
Hyperbolic Temperament as a Distinguishing Feature Between Borderline Personality Disorder and Mood Dysregulation

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Introduction

Given that mood disruption is a hallmark of borderline personality disorder (BPD) [1], it is not surprising that BPD often co-occurs with mood disorders. However, other evidence indicates clinically important distinctions between these forms of psychopathology [2–5]. In this chapter, we describe a model for distinguishing the features of BPD from mood disorders. We begin by reviewing the literature on their co-occurrence. We next survey evidence suggesting that associations between BPD and mood disorders can be understood in terms of a shared diathesis for negative affect. We then describe research on factors that distinguish patients with BPD from those with mood disorders and review theoretical models of BPD that may explain these factors. We then integrate existing research and theoretical models of BPD using a framework proposed by Zanarini and Frankenburg [6, 7] involving *hyperbolic temperament*. In this model, the distinguishing feature of BPD involves the tendency to exhibit intense emotional responses to certain kinds of evocative

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interpersonal experiences. We use existing data to evaluate the role of emotional hyperbole in the temperamental features of BPD and to isolate features of hyperbolic temperament that specifically distinguish BPD from depression. We conclude by discussing how the concept of hyperbolic temperament and these markers specifically can be used to guide differential diagnosis in clinical practice and contribute to a deeper understanding of the essential nature of BPD [7].

Co-occurrence of BPD and Mood Disorders

Because the prominent symptoms of both BPD and bipolar mood disorder involve mood instability, a number of authors have focused on the challenge of distinguishing these diagnoses. Some authors, such as Akiskal and colleagues [8–11], have suggested that BPD is best conceptualized as a bipolar spectrum disorder. However, the rates of bipolar disorder among individuals with BPD are in the range of 20–30 %, and the rates of BPD in individuals with bipolar disorders are lower than that [12–15]. Furthermore, the nature of BPD mood variability differs from bipolar disorder in a number of ways [16]. For example, mood changes in bipolar disorder tend to cycle at longer and less frequent intervals, and mood changes in BPD are more likely to be associated with interpersonal conflicts [3, 17, 18]. Individuals with BPD also show a different family prevalence pattern than disorders that are classified as bipolar spectrum, and these disorders seem to have an independent longitudinal course (i.e., neither disorder evolves into the other) [3]. This evidence suggests that BPD is more closely associated with unipolar than bipolar mood disturbance. Accordingly, in this chapter we will focus on how to distinguish BPD from unipolar depression specifically.

In contrast, the co-occurrence of major depressive disorder (MDD) among patients diagnosed with BPD is upwards of 80 % [15, 19]. However, this co-occurrence is particularly high among those diagnosed with severe cases of MDD (e.g., atypical or early onset MDD and MDD accompanied by angry outbursts) [14, 15, 19–24]. Interestingly, among patients diagnosed with MDD, BPD co-occurs in 8–24 % of cases. This pattern of co-occurrence would be consistent with the idea that as severity increases, the overlap between unipolar depression and BPD also increases. This is the pattern that would be expected if BPD were a severe form of MDD. In other words, if MDD and BPD existed on a continuous spectrum of severity of mood disturbance, individuals with MDD would be most likely to meet criteria for BPD if they were severe, whereas most individuals with BPD would meet criteria for MDD.

Co-occurrence as a Function of Negative Affectivity

From a personality and individual differences perspective, this pattern of co-occurrence might be taken to suggest shared etiological influences related to the personality trait negative affectivity or neuroticism [25, 26]. Negative affectivity is a relatively

stable and strongly heritable trait characterized by the experience of heightened negative emotions and sensitivity to stress [27–29]. Trait research consistently shows strong associations between BPD, depression, and negative affectivity [30–41]. For instance, in recent meta-analyses negative affectivity explained 29 % of the variance in BPD symptoms [42] and 22 % of the variance in MDD symptoms [33]. This literature suggests that findings from basic personality science can be useful for articulating the underlying dimension that largely explains their co-occurrence in clinical settings.

The concept of negative affectivity provides a reliable guidepost for behavior genetics research on the etiology of negative emotions common to BPD and MDD. Research from the behavior genetics literature suggests that both BPD and negative affectivity are highly heritable [43, 44]. This research also suggests that the genetic influences on BPD overlap with the genetic influences on MDD, indicating that some of the same genes associated with BPD are also associated with negative affectivity [45]. Critically, these influences are also shared with the personality trait negative affectivity [46]. Other research suggests that the common genes that influence negative affectivity, BPD, and MDD mediate encoding processes for serotonin [47]. It thus seems plausible that a temperamental disposition toward negative affectivity reflects a dysregulated serotonin system that contributes to a higher likelihood of MDD and BPD diagnosis and that individuals with a particularly high level of this trait are the most likely to have these co-occurring disorders.

Distinguishing BPD and Depression

Overall, it seems clear that BPD and MDD share the same core involving the experience of negative emotions [29, 40]. However, they are also distinct with respect to a number of clinically important factors. Existing research implies three primary distinctions: (a) impulse control [48], (b) the relative variability of negative moods [5], and (c) sensitivity to evocative events in the interpersonal environment [4].

Impulse Control

Impulsive behavior is diagnostic of BPD, such as in the DSM criterion involving "impulsivity in at least two areas that are potentially self-damaging [e.g., spending, sex, substance abuse, reckless driving, binge eating]" [1]. Borderline patients often present for services after an incident of impulsive behavior, such as self- or other-directed aggression. In contrast, although suicidality is an element of depression that often involves impulsivity, none of the diagnostic criteria for MDD directly imply impulsive behavior. Research on the underlying neurobiology of BPD supports the role of "impulsive aggression" as a diagnostic marker [49]. This research suggests that impulsive behavior in BPD is mediated by the serotonin system, as levels of central serotonin are negatively correlated with impulsive aggression in

BPD patients [50]. This appears to be associated with underactivity in cortical processes typically involved in constraining impulsive behavior [51].

Research on the empirical structure of psychopathology also supports the role of impulsivity in BPD. In this research, quantitative models are used to depict the degree to which different disorders covary, with this covariance represented in the form of shared factors. Two factors that commonly emerge are "internalizing," which explains covariation among mood and anxiety disorders and resembles the personality trait negative affectivity, and "externalizing," which explains covariation among substance use and antisocial disorders and includes the tendency to engage in impulsive behavior. In studies on the covariance of psychopathology, depression tends to be primarily related to an overarching internalizing factor without much of an influence by externalizing, whereas BPD relates to both internalizing and externalizing dispositions [52–55].

Emotional Dysregulation

A second underlying dimension of BPD involves affective instability [56] or "emotion dysregulation" [57]. Emotion dysregulation is represented in DSM criteria for BPD involving "affective instability due to a marked reactivity in mood" and "inappropriate, intense anger or difficulty controlling anger" [1]. This construct is central to the definition of BPD in Linehan's biosocial model [58, 59]. From the perspective of the biosocial model, difficulties regulating emotions are thought to develop as an interaction between (a) a biological vulnerability for heightened sensitivity, regulatory deficits, and difficulties recovering from emotional experiences and (b) an invalidating environment involving intolerance or shaming of emotional expressions and experiences, communicating to the individual that emotions should be coped with in the absence of support. Invalidation contributes to a failure to learn how to cope with emotions and thus promotes further invalidation. Invalidation can take the form of traumatic life experiences [60–63] as well as more subtle forms of emotional invalidation (e.g., a parent telling a crying child that he or she is not sad) [59]. When the individual feels invalidated, he or she may exhibit intense "storms" of negative affect. Accordingly, the emotional experience of individuals with BPD often varies greatly depending on environmental context. In contrast, negative moods tend to be fairly stable throughout a major depressive episode. In summary, relative to mood disorders, mood disturbance is more severe, more volatile, and more dependent on interpersonal context for individuals with BPD [4, 5, 64].

Interpersonal Sensitivity

The feature of individuals with BPD that is perhaps most readily observable is sensitivity to interpersonal context and the tendency to dysregulate in relationships. Interpersonal sensitivity is reflected in the DSM criterion involving "a pattern of

unstable and intense interpersonal relationships characterized by alternating between extremes of idealization and devaluation" [1]. Given the tendency for borderline pathology to play out in relationships, Gunderson and Lyons-Ruth [65] have focused on interpersonal sensitivity as the core characteristic of BPD. From this perspective, innate differences in interpersonal sensitivity render individuals differentially responsive to problems in attachment relationships, including attachment figures' emotional dysregulation. These differences in interpersonal sensitivity may be particularly pronounced in intimate interpersonal relationships (e.g., attachment relationships), in which the emotions of participants in the relationship may be more attuned [66, 67]. This pattern may help explain the notorious challenges associated with the treatment of BPD, in particular the need to attend to both positive and negative aspects of the therapeutic relationship.

An Integrative Perspective on BPD

In both Linehan's [59] biosocial model and Gunderson's and Lyons-Ruth's [65] interpersonal sensitivity model of BPD, impulsive behavior occurs in the context of interpersonally provoked emotion dysregulation, and the interaction between interpersonal and affective disturbance is dynamic and mutually influential. In other words, even though basic dimensions underlying borderline pathology can be parsed as individual differences dimensions, at the level of the individual patient, these etiological factors play out in meaningfully patterned processes. For instance, an interpersonally sensitive child attached to an emotionally volatile parent may, over time, develop his or her own pattern of variable emotional experience. The absence of a stable affective experience may, in turn, inhibit the child's potential to develop a stable sense of self. Without a stable base of interpersonal or affective experience, interpersonally sensitive individuals may have difficulty accurately anticipating the events in their interpersonal environments. As a result, interpersonal situations often catch them off-guard and they may react impulsively to them. They may then bring this pattern of dysregulated and impulsive behaviors to future relationships. In doing so, they may inadvertently elicit similar sorts of dysregulating interpersonal experiences that caused distress earlier in development. The goal of the rest of this chapter is to articulate a model that attempts to integrate these features and to evaluate the potential of this model to provide a framework for the differential diagnosis of BPD and mood disorders.

Emotional Hypochondriasis, Hyperbolic Temperament, and Kindling Events

Unlike models that focus more or less on one of these features as the most central distinguishing characteristic, the hyperbolic model of BPD proposed by Zanarini and Frankenburg [6, 7] attempts to integrate them into a comprehensive model of

the core features of BPD. Zanarini and Frankenburg [6, 68] describe the characteristic manner in which individuals with BPD respond to emotionally evocative events as emotional hypochondriasis or "the transformation of unbearable feelings of rage, sorrow, shame, and/or terror into unremitting attempts to get others to pay attention to the enormity of the emotional pain that one feels" [68]. For example, when individuals with BPD experience negative emotions (e.g., sadness), they often experience them so intensely that they feel overwhelmed and respond by maladaptively attempting to draw in another person to help them regulate their feelings (e.g., by furious insistence). This pattern is characteristic of the disorder; borderline patients can alternate between reeling from intense inner pain and engaging in drastic behaviors aimed at remedying that pain. Research supports that individuals with BPD report significantly more frequent use of emotional hypochondriasis, which is classified as "immature" in taxonomies of defense [69], than those with other personality disorders [70].

Zanarini and Frankenburg [7] assert that emotional hypochondriasis is predisposed by a vulnerable or "hyperbolic" temperament. This concept is similar to negative affectivity; the trait or spectrum that we argued above seems to explain the covariation between BPD and mood disorders. However, hyperbolic temperament differs from negative affectivity in two ways. First, hyperbolic temperament involves the tendency to experience intense inner pain (i.e., profound negative affects) *in response to perceived interpersonal disappointment or frustration*. In contrast, negative affectivity implies a heightened tendency to experience negative emotions in general, whether or not they are reactions to specific kinds of environmental events. Second, hyperbolic temperament is conceptualized as a product of the disposition to experience negative emotions coupled with perceived maltreatment during development [71]. This pattern is thought to play out in particular when the individual becomes dysregulated. This dysregulation, in turn, leads to immediate bids for others to validate the individual's feelings. However, these bids are often drastic and impulsive and may evoke behaviors from others that tend to invalidate rather than soothe the individual's distress, thus leading to a vicious cycle of further dysregulation [6, 7]. In contrast, negative affectivity is typically conceptualized as an endogenous, heritable disposition that is largely stable across situations [28, 72].

As an initial step in testing aspects of the hyperbolic model, Hopwood and colleagues evaluated a measure designed by Zanarini to define and assess the construct, the *Hyperbolic Temperament Questionnaire* (HTQ) [73]. In this study, 11 items formed a scale that is conceptually associated with hyperbolic temperament (Table 7.1). Strong associations were observed between scores on this measure and BPD symptoms in both normal ($r = .53$) and clinical ($r = .63$) populations. This study provided initial support for the validity of hyperbolic temperament, established a measurement tool for further study, and helped articulate the elements of hyperbolic temperament. In particular, the items on this scale involved the experience of negative moods (e.g., "I am a nervous or anxious person") as well as hyperbolic responses to these moods (e.g., "I frequently feel that people are insensitive to my feelings"). Thus, consistent with Zanarini and Frankenburg's original theoretical work, such features coalesce as a meaningful dimension and explain a substantial proportion of variation in BPD symptoms.

Table 7.1 Item-level correlations between HTQ, BPD, and depression

Content	*r* (BPD)	*r* (depression)
I get upset very easily	.44	.35
I often make a big deal out of things	.36	.29
I cannot forget my pain or problems	.41	.37
I have a great deal of trouble letting things go	.33	.30
I frequently feel that people are insensitive to my feelings	.38	.35
I am deeply attached to my past and all its painful memories	.41	.40
My feelings are very easily hurt	.29	.29
I am a very sensitive person	.24	.25
I am a nervous or anxious person	.41	.45
I am a fretful person	.31	.34
I am often fearful or frightened	.38	.43

Zanarini and Frankenburg [7] propose that BPD symptoms result when individuals with hyperbolic temperaments experience kindling events or interpersonal transactions that are emotionally invalidating for the individual experiencing them. For example, someone with a hyperbolic temperament may experience intense and overwhelming feelings of sadness in response to perceived abandonment by an adult romantic partner. This event would cue the intense inner pain characteristic of BPD and, thereby, frantic means to cope. In this situation, such an individual might lash out angrily or engage in desperate clinging and pleading, prompting an actual abandonment by the partner.

The intensity of kindling events and hyperbolic vulnerability would be anticipated to explain the severity of BPD symptoms. To test this hypothesis, we examined whether the interaction between kindling events and hyperbolic temperament was associated with BPD symptoms. Using data from the HTQ validation study, we assessed hyperbolic temperament using the HTQ and kindling events using *Childhood Trauma Questionnaire* (CTQ) [74], an assessment of child maltreatment, an interpersonal stressor that is common in the histories of individuals with BPD [75]. We found that the interaction between hyperbolic temperament and kindling events provided a significant incremental influence ($\beta = .11$) on BPD symptom severity in a regression model controlling for the significant main effects of hyperbolic temperament ($\beta = .54$) and maltreatment ($\beta = .25$). Interestingly, this was not the case for any other personality disorder. This finding is consistent with the hypothesis that hyperbolic temperament interacts with kindling events to produce BPD symptoms and suggests some specificity of that process to BPD.

Temperamental and Acute Symptoms of BPD

Zanarini and colleagues [76, 77] observed important temporal differences among BPD symptoms of relevance to the hyperbolic model. They conceptualize these differences in terms of two types of BPD symptoms: acute and temperamental.

Acute symptoms include impulsive means of dealing with pervasive negative emotions (e.g., non-suicidal self-injury) and the more active interpersonal symptoms of BPD (e.g., acting in a demanding or devaluative manner); they typically remit relatively quickly and, because they often prompt the individual to seek treatment, are the best markers of acute BPD. In contrast, temperamental symptoms are associated with chronic dysphoria and concerns with interpersonal dependency and fears of abandonment; these symptoms remit more slowly and are associated with long-term psychosocial impairment.

Acute and temperamental symptoms would be expected to differentially relate to the predisposing factors of BPD. Specifically, temperamental symptoms would be expected to reflect latent features of hyperbolic temperament that tend to endure in the experiences of individuals with BPD. In contrast, the acute type of BPD symptoms are thought to be relatively more responsive to the dynamics of interpersonal situations and life circumstances. To examine whether hyperbolic temperament was more associated with stable or acute symptoms, we analyzed the association between these three constructs in participants ($N = 309$) of year 10 of the McLean Study of Adult Development (MSAD) [76]. Temperamental symptoms had a strong association with hyperbolic temperament ($\beta = .54$, $p < .001$), while the association between hyperbolic temperament and acute symptoms was not significant with temperamental symptoms controlled. These results suggest a unique association between hyperbolic temperament and temperamental BPD symptoms vis-à-vis acute BPD symptoms. This connects the hyperbolic model to important temporal distinctions in BPD symptoms by linking temperamental vulnerability to the more enduring features of the disorder involving inner pain and enmeshment.

Differential Diagnosis of BPD and MDD

The overall goal of this chapter has been to develop the potential of the hyperbolic model to address the specific problem of distinguishing BPD from other mood disorders, particularly MDD. Although our thesis has been that hyperbolic temperament captures clinically important information that can help with this differential diagnosis, it is notable that depressed individuals also have some features similar to those that characterize hyperbolic temperament, such as a heightened tendency to experience negative moods. Indeed, Hopwood and colleagues [73] found that hyperbolic temperament was strongly associated with both BPD and depression. This finding prompted us to examine the specificity of hyperbolic temperament so as to shed further light on which aspects most differentiate depression and BPD.

To understand which aspects of hyperbolic temperament were most specific to BPD, we correlated each item of the hyperbolic scale of the HTQ with BPD (as measured by *Personality Diagnostic Questionnaire – 4* [PDQ-4]) [78] and depression (as measured by *Center for Epidemiological Studies Depression Scale* [CESD]) [79] using data from the original study [73]. In Table 7.1, hyperbolic features are ordered according to their associations with these two constructs. Those items most

highly correlated with BPD relative to depression are at the top of the list. These items have more to do with emotional reactivity, whereas those items at the bottom of the list that are more correlated with depression contain content more associated with generalized negative affect. In other words, emotional reactivity seems to be the aspect of hyperbolic temperament that most differentiates BPD from unipolar depression. In other words, the general tendency to experience negative emotions may explain why BPD and MDD co-occur, whereas the tendency of individuals with BPD to have variable moods due to reactivity to intense interpersonal situations provides the basis for distinguishing these diagnoses.

Conclusion

In this chapter, we reviewed a hyperbolic model in which the core characteristic of BPD involves maladaptive emotional responses to an interaction between kindling events and hyperbolic temperament (i.e., emotional hypochondriasis). We also extended this model empirically in three ways. First, we showed that the interaction between emotional hyperbole and kindling events specifically indicates borderline psychopathology. Second, we showed that hyperbolic temperament is most strongly related to the stable, temperamental aspects of BPD involving internal dysphoria and interpersonal dependency that are responsible for ongoing psychosocial impairment and less related to the acute aspects of BPD involving impulsive behaviors and interpersonal patterns, such as entitlement and manipulation that tend to be the initial focus of treatment. Third, we identified key markers of hyperbolic temperament and how they are associated with BPD relative to depression. In particular, we showed that the association between BPD and MDD can be largely explained by a vulnerability to negative moods, whereas the difference between these disorders involves emotional reactivity to stressful interpersonal situations.

We have argued that the hyperbolic model provides an integrative framework for differentiating BPD from depression and other mood problems. This framework clarifies some central conceptual problems in the diagnosis of BPD and provides a useful model for differential diagnosis in applied settings. However, our knowledge about hyperbolic temperament as a construct remains limited, raising a number of theoretical challenges as well as directions for future research. For example, although studies exist on the stability of BPD [80–88], there is little research on the stability of hyperbolic temperament. Similarly, evidence about how hyperbolic temperament and kindling events interact with each other over time is limited. Finally, methods for addressing aspects of hyperbolic temperament clinically remain to be developed and tested. Nevertheless, the hyperbolic model provides a promising conceptualization of BPD that can inform differential diagnosis, frame treatment, and offer insights or directions for future research.

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References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013.
2. Koenigsberg HW, Harvey PD, Mitropoulou V, Schmeidler J, New AS, Goodman M. Characterizing affective instability in borderline personality disorder. Am J Psychiatry. 2002;159:784–8.
3. Paris J, Gunderson J, Weinberg I. The interface between borderline personality disorder and bipolar spectrum disorders. Compr Psychiatry. 2007;48:145–54.
4. Sadikaj G, Russell JJ, Moskowitz DS, Paris J. Affect dysregulation in individuals with borderline personality disorder: persistence and interpersonal triggers. J Pers Assess. 2010;92: 490–500.
5. Trull TJ, Solhan MB, Tragesser SL, Jahng S, Wood PK, Piasecki TM, et al. Affective instability: measuring a core feature of borderline personality disorder with ecological momentary assessment. J Abnorm Psychol. 2008;117:647–61.
6. Zanarini MC, Frankenburg FR. Pathways to the development of borderline personality disorder. J Pers Disord. 1997;11:93–104.
7. Zanarini MC, Frankenburg FR. The essential nature of borderline psychopathology. J Pers Disord. 2007;21:518–35.
8. Akiskal HS. Borderline: an adjective still in search of a noun. In: Silver D, Rosenbluth M, editors. Handbook of borderline disorders. Madison: International Universities Press; 1992. p. 155–76.
9. Akiskal HS. The temperamental borders of affective disorders. Acta Psychiatr Scand Suppl. 1994;89:32–7.
10. Akiskal HS. The bipolar spectrum in psychiatric and general medical practice. Primary Psychiatry. 2004;11:30–5.
11. Perugi G, Toni C, Travierso MC, Akiskal HS. The role of cyclothymia in atypical depression: toward a data-based reconceptualization of the borderline-bipolar II connection. J Affect Disord. 2003;73:87–98.
12. Gunderson JG, Weinberg I, Daversa MT, Kueppenbender KD, Zanarini MC, Shea MT, et al. Descriptive and longitudinal observations on the relationship of borderline personality disorder and bipolar disorder. Am J Psychiatry. 2006;163:1173–8.
13. Garno JL, Goldberg JF, Ramirez PM, Ritzler BA. Bipolar disorder with comorbid cluster B personality disorder features: impact on suicidality. J Clin Psychiatry. 2005;66:339–45.
14. Tedlow J, Leslie V, Keefe BR, Alpert J, Nierenberg AA, et al. Axis I and Axis II disorder comorbidity in unipolar depression with anger attacks. J Affect Disord. 1999;52:217–23.
15. Zanarini MC, Frankenburg FR, Dubo ED, Sickel AE, Trikha A, Levin A, et al. Axis I comorbidity of borderline personality disorder. Am J Psychiatry. 1998;155:1733–9.
16. Paris J. Borderline or bipolar? Distinguishing borderline personality disorder from bipolar spectrum disorders. Harv Rev Psychiatry. 2004;12:140–5.
17. Reich DB, Zanarini MC, Fitzmaurice G. Affective lability in bipolar disorder and borderline personality disorder. Compr Psychiatry. 2012;53:230–7.
18. Reich DB, Zanarini MC, Hopwood CJ, Thomas KM, Fitzmaurice G. Comparison of affective instability in borderline personality disorder and bipolar disorder using a self-report measure. Personal Ment Health. 2014;8:143–50.
19. Zanarini MC, Frankenburg FR, Hennen J, Reich DB, Silk KR. Axis I comorbidity in patients with borderline personality disorder: 6-year follow-up and prediction of time to remission. Am J Psychiatry. 2004;161:2108–14.
20. Fava M, Alpert JE, Borus JS, Nierenberg AA, Pava JA, Rosenbaum JF. Patterns of personality disorder comorbidity in early-onset versus late-onset major depression. Am J Psychiatry. 1996;153:1308–12.

21. Petersen T, Hughes M, Papakostas GI, Kant A, Fava M, Rosenbaum JF, et al. Treatment-resistant depression and Axis II comorbidity. Psychother Psychosom. 2002;71:269–74.
22. Rogers JH, Widiger TA, Krupp A. Aspects of depression associated with borderline personality disorder. Am J Psychiatry. 1995;152:268–70.
23. Tadić A, Wagner S, Hoch J, Başkaya Ö, von Cube R, Skaletz C, et al. Gender differences in axis I and axis II comorbidity in patients with borderline personality disorder. Psychopathology. 2009;42:257–63.
24. Zimmerman M, Mattia JI. Axis I diagnostic comorbidity and borderline personality disorder. Compr Psychiatry. 1999;40:245–52.
25. Reichborn-Kjennerud T, Czajkowski N, Røysamb E, Ørstavik RE, Neale MC, Torgersen S, Kendler KS. Major depression and dimensional representations of DSM-IV personality disorders: a population-based twin study. Psychol Med. 2010;40:1475–84.
26. Wright AGC, Thomas KM, Hopwood CJ, Markon KE, Pincus AL, Krueger RF. The hierarchical structure of DSM-5 pathological personality traits. J Abnorm Psychol. 2012; 121:951–7.
27. Clark LA, Watson D. Temperament: an organizing paradigm for trait psychology. In: Leary MR, Hoyle RH, editors. Handbook of individual differences in social behavior. New York: Guilford Press; 2009. p. 265–86.
28. Costa PT, McCrae RR. The five-factor model, five-factor theory, and interpersonal psychology. In: Horowitz LM, Strack S, editors. Handbook of interpersonal psychology: theory, research, assessment, and therapeutic interventions. Hoboken: Wiley; 2011. p. 91–104.
29. Widiger TA. Neuroticism. In: Leary MR, Hoyle RH, editors. Handbook of individual differences in social behavior. New York: Guilford Press; 2009. p. 129–46.
30. Clarkin JF, Hull JW, Cantor J, Sanderson C. Borderline personality disorder and personality traits: a comparison of SCID-II BPD and NEO-PI. Psychol Assess. 1993;5:472.
31. Hopwood CJ, Wright AGC, Zanarini MC. Associations between changes in normal personality traits and borderline personality disorder symptoms over 16 years. Article submitted.
32. Jylhä P, Mantere O, Melartin T, Suominen K, Vuorilehto M, Arvilommi P, et al. Differences in neuroticism and extraversion between patients with bipolar I or II and general population subjects or major depressive disorder patients. J Affect Disord. 2010;125:42–52.
33. Kotov R, Gamez W, Schmidt F, Watson D. Linking "big" personality traits to anxiety, depressive, and substance use disorders: meta-analysis. Psychol Bull. 2010;136:768–821.
34. Krueger RF, Eaton NR, Derringer J, Markon KE, Watson D, Skodol AE. Personality in DSM–5: helping delineate personality disorder content and framing the metastructure. J Pers Assess. 2011;93:325–31.
35. Lahey BB. Public health significance of neuroticism. Am Psychol. 2009;64:241–56.
36. Livesley J. Toward a genetically-informed model of borderline personality disorder. J Pers Disord. 2008;22:42–71.
37. Morey LC, Zanarini MC. Borderline personality: traits and disorder. J Abnorm Psychol. 2000;109:733–7.
38. Trull TJ, Widiger TA, Lynam DR, Costa PT. Borderline personality disorder from the perspective of general personality functioning. J Abnorm Psychol. 2003;112:193–202.
39. Widiger TA, Livesley WJ, Clark LA. An integrative dimensional classification of personality disorder. Psychol Assess. 2009;21:243–55.
40. Widiger TA, Trull TJ. Personality and psychopathology: an application of the five-factor model. J Pers. 1992;60:363–93.
41. Wilberg T, Urnes Ø, Friis S, Pedersen G, Karterud S. Borderline and avoidant personality disorders and the five-factor model of personality: a comparison between DSM-IV diagnoses and NEO-PI-R. J Pers Disord. 1999;13:226–40.
42. Samuel DB, Widiger TA. A meta-analytic review of the relationships between the five-factor model and DSM-IV-TR personality disorders: a facet level analysis. Clin Psychol Rev. 2008;28:1326–42.

43. Wray NR, Birley AJ, Sullivan PF, Visscher PM, Martin NG. Genetic and phenotypic stability of measures of neuroticism over 22 years. Twin Res Hum Genet. 2007;10:695–702.
44. Distel MA, Trull TJ, Derom CA, Thiery EW, Grimmer MA, Martin NG, et al. Heritability of borderline personality disorder features is similar across three countries. Psychol Med. 2008;38:1219–29.
45. Distel MA, Trull TJ, Willemsen G, Vink JM, Derom CA, Lynskey M, et al. The five-factor model of personality and borderline personality disorder: a genetic analysis of comorbidity. Biol Psychiatry. 2009;66:1131–8.
46. Kendler KS, Myers J. The genetic and environmental relationship between major depression and the five-factor model of personality. Psychol Med. 2010;40:801–6.
47. Maurex L, Zaboli G, Öhman A, Åsberg M, Leopardi R. The serotonin transporter gene polymorphism (5-HTTLPR) and affective symptoms among women diagnosed with borderline personality disorder. Eur Psychiatry. 2010;25:19–25.
48. Links PS, Heslegrave R, van Reekum R. Impulsivity: core aspect of borderline personality disorder. J Pers Disord. 1999;13:1–9.
49. Koenigsberg HW, Siever LJ. Borderline personality disorder. In: Squire L, editor. Encyclopedia of neuroscience. New York: Elsevier; 2008. p. 283–7.
50. Goodman M, New AS. Impulsive aggression in borderline personality disorder. Curr Psychiatry Rep. 2000;2:56–61.
51. Soloff PH, Meltzer CC, Greer PJ, Constantine D, Kelly TM. A fenfluramine-activated FDG-PET study of borderline personality disorder. Biol Psychiatry. 2000;47:540–7.
52. Eaton NR, Krueger RF, Keyes KM, Skodol AE, Markon KE, Grant BF, et al. Borderline personality disorder co-morbidity: relationship to the internalizing-externalizing structure of common mental disorders. Psychol Med. 2011;41:1041–50.
53. Kendler KS, Aggen SH, Knudsen GP, Røysamb E, Neale MC, Reichborn-Kjennerud T. The structure of genetic and environmental risk factors for syndromal and subsyndromal common DSM-IV axis I and all axis II disorders. Am J Psychiatry. 2011;168:29–39.
54. Røysamb E, Kendler KS, Tambs K, Ørstavik RE, Neale MC, Aggen SH, et al. The joint structure of DSM-IV Axis I and Axis II disorders. J Abnorm Psychol. 2011;120:198–209.
55. Wright AGC, Krueger RF, Hobbs MJ, Markon KE, Eaton NR, Slade T. The structure of psychopathology: toward an expanded quantitative empirical model. J Abnorm Psychiatry. 2013;122:281–94.
56. Siever LJ, Davis KL. A psychobiological perspective on the personality disorders. Am J Psychiatry. 1991;148:1647–58.
57. Gratz KL, Dixon-Gordon KL, Breetz A, Tull M. A laboratory-based examination of responses to social rejection in borderline personality disorder: the mediating role of emotion dysregulation. J Pers Disord. 2013;27:157–71.
58. Crowell SE, Beauchaine TP, Linehan MM. A biosocial developmental model of borderline personality: elaborating and extending Linehan's theory. Psychol Bull. 2009;135:495–510.
59. Linehan MM. Cognitive-behavioral treatment of borderline personality disorder. New York: Guilford Press; 1993.
60. Battle CL, Shea M, Johnson DM, Yen S, Zlotnick C, Zanarini MC, et al. Childhood maltreatment associated with adult personality disorders: findings from the collaborative longitudinal personality disorders study. J Pers Disord. 2004;18:193–211.
61. Kaehler LA, Freyd JJ. Borderline personality characteristics: a betrayal trauma approach. Psychol Trauma. 2009;1:261–8.
62. Kaehler LA, Freyd JJ. Betrayal trauma and borderline personality characteristics: gender differences. Psychol Trauma. 2012;4:379–85.
63. Löffler-Stastka H, Szerencsics M, Blüml V. Dissociation, trauma, affect regulation and personality in patients with a borderline personality organization. Bull Menniger Clin. 2009;73: 81–98.
64. Hopwood CJ, Wright AGC, Ansell EB, Pincus AL. The interpersonal core of personality pathology. J Pers Disord. 2013;27:270–95.

65. Gunderson JG, Lyons-Ruth K. BPD's interpersonal hypersensitivity phenotype: a gene-environment-developmental model. J Pers Disord. 2008;22:22–41.
66. Bowlby J. Attachment and loss, Attachment, vol. I. London: Hogarth; 1969.
67. Sullivan HS. The interpersonal theory of psychiatry. New York: Norton; 1953.
68. Zanarini MC, Frankenburg FR. Emotional hypochondriasis, hyperbole, and the borderline patient. J Psychother Pract Res. 1994;3:25–36.
69. Vaillant GE. Ego mechanisms of defense: a guide for clinicians and researchers. Washington, DC: American Psychiatric Press; 1992.
70. Zanarini MC, Frankenburg FR, Fitzmaurice G. Defense mechanisms reported by patients with borderline personality disorder and Axis II comparison subjects over 16 years of prospective follow-up: description and prediction of recovery. Am J Psychiatry. 2013;170:111–20.
71. Hopwood CJ, Zanarini MC. The contributions of neuroticism and childhood maltreatment to hyperbolic temperament. J Pers Disord. 2012;26:815–20.
72. McCrae RR, Costa PT. The five-factor theory of personality. In: Leary MR, Hoyle RH, editors. Handbook of individual differences in social behavior. New York: Guilford Press; 2009. p. 159–81.
73. Hopwood CJ, Thomas KM, Zanarini MC. Hyperbolic temperament and borderline personality disorder. Pers Ment Health. 2012;6:22–32.
74. Bernstein DP, Fink L. Childhood trauma questionnaire: a retrospective self-report manual. San Antonio: The Psychological Corporation; 1998.
75. Zanarini MC, Ruser TF, Frankenburg FR, Hennen J, Gunderson JG. Risk factors associated with the dissociative experiences of borderline patients. J Nerv Ment Dis. 2000;188:26–30.
76. Zanarini MC, Frankenburg FR, Hennen J, Reich DB, Silk KR. The McLean Study of Adult Development (MSAD): overview and implications of the first six years of prospective follow-up. J Pers Disord. 2005;19:505–23.
77. Zanarini MC, Frankenburg FR, Reich D, Silk KR, Hudson J, McSweeney L. The subsyndromal phenomenology of borderline personality disorder: a 10-year follow-up study. Am J Psychiatry. 2007;164:929–35.
78. Hyler SE. Personality diagnostic questionnaire-4 (PDQ-4). New York: New York State Psychiatric Institute; 1994.
79. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. Appl Psychol Meas. 1977;1:384–401.
80. Hopwood CJ, Donnellan MB, Blonigen DM, Krueger RF, McGue M, Iacono WG, et al. Genetic and environmental influences on personality trait stability and growth during the transition to adulthood: a three-wave longitudinal study. J Pers Soc Psychol. 2011;100: 545–56.
81. Hopwood CJ, Newman DA, Donnellan MB, Markowitz JC, Grilo CM, Sanislow CA, et al. The stability of personality traits in individuals with borderline personality disorder. J Abnorm Psychol. 2009;118:806–15.
82. McGlashan TH, Grilo CM, Sanislow CA, Ralevski E, Morey LC, Gunderson JG, et al. Two-year prevalence and stability of individual DSM-IV criteria for schizotypal, borderline, avoidant, and obsessive-compulsive personality disorders: toward a hybrid model of Axis II disorders. Am J Psychiatry. 2005;162:883–9.
83. Sanislow CA, Little TD, Ansell EB, Grilo CM, Daversa M, Markowitz JC, et al. Ten-year stability and latent structure of the DSM–IV schizotypal, borderline, avoidant, and obsessive-compulsive personality disorders. J Abnorm Psychol. 2009;118:507–19.
84. Shea MT, Stout R, Gunderson JG, Morey LC, Grilo CM, McGlashan T, et al. Short-term diagnostic stability of schizotypal, borderline, avoidant, and obsessive-compulsive personality disorders. Am J Psychiatry. 2002;159:2036–41.
85. Zanarini MC, Frankenburg FR, Reich DB, Fitzmaurice G. Time to attainment of recovery from borderline personality disorder and stability of recovery: a 10-year prospective follow-up study. Am J Psychiatry. 2010;167:663–7.

86. Zanarini MC, Frankenburg FR, Reich DB, Fitzmaurice G. Attainment and stability of sustained symptomatic remission and recovery among patients with borderline personality disorder and axis II comparison subjects: a 16-year prospective follow up study. Am J Psychiatry. 2012;169:476–83.
87. Grilo CM, Becker DF, Anez LM, McGlashan TH. Diagnostic efficiency of DSM-IV criteria for borderline personality disorder: an evaluation in Hispanic men and women with substance use disorders. J Consult Clin Psychol. 2004;72(1):126–31. PMID: 14756622.
88. Morey LC, Hopwood CJ. Stability and change in personality disorders. Annu Rev Clin Psychol. 2013;9:499–528. doi:10.1146/annurev-clinpsy-050212-185637.

Chapter 8
The Integration of Mood, Behavior, and Temperament in Mood Spectrum Disorders

Diogo R. Lara, Gustavo L. Ottoni, Luisa W. Bisol, and Hudson W. de Carvalho

Introduction

The scientific model has produced enormous advances in many fields of knowledge by applying an analytical and mechanistic approach. However, the reductionism of traditional science may be insufficient and sometimes ill-advised when studying complex systems in which the relations between their parts are as important as the parts themselves. This is the case of whole organisms or some of its systems, such as the nervous and the immune systems. Their plasticity is essential to process information and to function adequately.

Building knowledge is favored by using both deductive and inductive thinking in a dialectical interplay to transform data into information and information into principles. Models can then be created to accommodate data, information, and principles within a coherent perspective that can be tested and polished to evolve or succumb.

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This has been the approach adopted to create and study the Affective and Emotional Composite Temperament (AFECT) model [1]. Our aim has been to develop an integrated, useful, and valid framework to understand mood, behavior, emotions, and core personality traits applicable for both adaptive and dysfunctional situations. This is in sharp contrast to the purported atheoretical and descriptive approach of diagnostic manuals such as the DSM and CID, which abstain from defining healthy mental functioning and arbitrarily adopt multiple categories of "discrete mental disorders."

The AFECT model combines two major conceptual views of temperament and personality models. One conceives the specific dimensional traits (i.e., the "parts" using an analytical approach) that compose personality. This line of thinking has been adopted in most frameworks, including Hippocrates/Galen's four humors, the Big Five model, Gray's Activation and Inhibition systems, Cloninger's Temperament and Character model, Zuckerman's personality model, and Rothbart's Temperament model among others, and by those who study a single trait (e.g., coping, resilience, anger…). These models have greatly advanced the field of psychology, but in our opinion they are not sufficiently coherent, simple, or attached to suitable language and instruments to be clinically useful. Of note, the NIMH perspective adopts a similar approach [2]. The emotional traits of the AFECTS system are inspired by these models and are intended to improve (1) comprehension by applying a systems-based framework and (2) clinical utility by using simple terms (e.g., fear, anger, energy, control, coping) and providing a relatively short (60 items) self-report assessment, the AFECT scale (AFECTS).

The other conceptual view adopts a global perspective of temperament and personality proposing categories that unite several aspects together, i.e., a typology. Our main reference is the original proposal by Kraepelin of the fundamental states (manic, cyclothymic, irritable, and melancholic), recently revised as affective temperaments by Akiskal with new labels (manic turned into hyperthymic, melancholic into depressive) and the inclusion of the anxious type [3]. Cloninger has also produced a typology that derives from the combination of dimensional scores of temperament (e.g., high novelty seeking and harm avoidance and low reward dependence form the explosive/borderline type) [4]. This is similar to the ancient approach of 2×2 crossing between the two axes of humidity and temperature (low and high) producing the choleric, phlegmatic, melancholic, and sanguine types [5]. Over time, many personality typologies have been created. The most popular of these pertains to astrology, which adopted Empedocles' view of the world as composed of the elements of fire, water, earth, and air, similarly to Hippocrates.

We conceive temperament as an integrated concept reflecting the basis of emotions, behavior, cognition, and personality. Since emotions, behavior, and cognition are coherently associated and are influenced by one's temperament, the utility of separating them is more important for therapeutic than diagnostic purposes. A more complete understanding of personality and the structure of the mind requires a systems-based approach at many levels: individual, social (family, groups/friends, community), and conceptual (society, world/intellect, and universe/existence) [6], but this is not the focus of this chapter.

The AFECT Model: A Systems-Based Approach

The first basic notion in the AFECT model is that the brain-mind forms a system that belongs to a whole organism. Although commonly called the nervous system, the word "nervous" is usually regarded as synonymous to "brain and nerves," and little attention is paid to the word "system." We share the view of the brain and mind as entangled and complementary (i.e., two incompatible descriptions have to be used to describe something in full), in contrast to the prevailing materialist notion that mental and psychological processes are emergent properties of an organism [7]. This view facilitates the understanding of holistically correlated behavior on different levels of systemic complexity.

Since systems theories such as Bertalanffy's are complex and have rarely been a focus of study in medicine and psychology, we developed a simplified notion of a living system, named AIS-2C (Activation, Inhibition, Sensitivity, Control, and Coping) (Fig. 8.1). This acronym should be pronounced as "eyes to see" to play with the concept that the recognition of a system demands a "transcendent" view. In short, a living system is composed of two main orthogonal "vectors" (Activation and Inhibition), managed with Control, has Sensitivity to the environment and an intrinsic ability to cope with it by processing information (cognition) and being able to change (plasticity). Other domains recently conceived are Harmony and Stability, which depend mostly on the five core AIS-2C elements and describe how the system behaves over time. When useful, the most common relationships between these parts can then be classified into major patterns, facilitating synthetic communication by adding a global perspective.

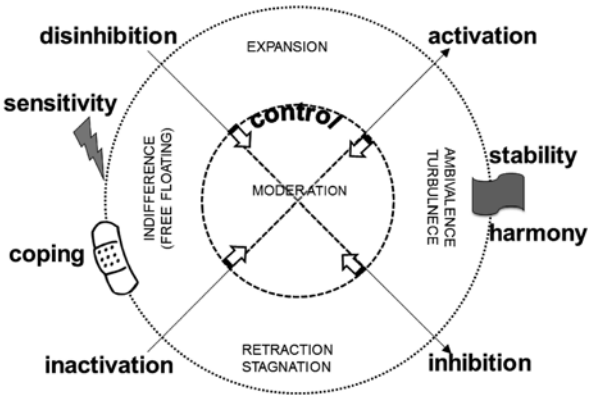

Fig. 8.1 The AIS2C (Activation-Inhibition-Sensitivity-Coping-Control) matrix. Activation and Inhibition are the main vectors, which are regulated by control. Combinations of Activation and Inhibition levels produce the main synthetic results of expansion, stagnation, ambivalence, indifference, and moderation. Sensitivity and Coping refer to how the system responds to environmental adversity. Stability and Harmony are general properties that result from the other features of the system

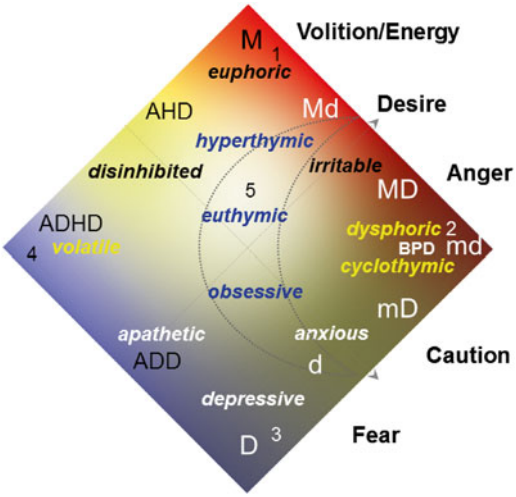

Fig. 8.2 Temperament matrix producing affective temperaments (in *italics*), mood/energy disorders (M, D, md, ADHD) and other psychiatric disorders (numbers). Higher Control is represented as "C". Low Sensitivity and Anxiety and high Coping and Stability are represented by the *white shade. 1* configuration prone to externalized disorders, such as mania; bipolar I disorder; antisocial, narcissistic, and histrionic personality disorders; intermittent explosive disorder; excessive and compulsive behaviors associated with high desire, such as drug abuse and dependence (including cigarette smoking), buying, and sex; *2* configuration prone to externalized/internalized disorders, such as mixed mood states, bipolar II disorder, bulimia, PTSD, panic, borderline (BPD) and paranoid personality disorders, mixed types of OCD, some attention deficit disorder, drug abuse to decrease sensitivity, such as alcohol and benzodiazepines; *3* configuration prone to internalized disorders, such as depression, generalized anxiety, social phobia, panic, inhibited types of OCD, cluster C personality disorders; *4* configuration prone to ADHD, learning disorders (towards the bottom), oppositional defiant disorder (towards the top); *5* configuration prone to good mental health, with low risk for development of psychiatric disorders, and high chance of recovery if a psychiatric disorder develops, e.g., due to acute stress

The AIS-2C principles can be applied to systems by simply adapting the terms. In the case of temperament (Fig. 8.2), the AIS-2C was translated as emotional traits, which putatively reflect relevant neurobiological and behaviors subsystems. Activation refers to the dimensions of Energy/Volition, Desire, and Anger. This separation became necessary and useful to enrich the understanding of how behavior is motivated and initiated. Volition (a more adequate term for languages of Latin origin) is the basic Energy (better term for Anglo-Saxon languages) to drive action, has an inbuilt positive bias, and is not focused on immediate reward. This energy allows processes to be carried on and underlies activities such as getting up from bed, doing routine actions, interacting with others, working, and so on. In contrast, Desire is the instinctive attraction to reward, originally to food and sex, but expanded during civilization to drugs of abuse, power, games/gambling, vanity, and other "objects." Anger arises when the Desire is not satisfied and may be adaptive

to overcome the barriers to reach the desired object. Inhibition reflects Fear (the reverse of audacity) and Caution (the reverse of impulsivity), which are important for avoidance and protection, respectively. Emotional Sensitivity is how the system reacts to straining events, frustration, and interpersonal stress. Control is the ability to monitor the environment (attention) and to regulate the expression of Activation and Inhibition, thereby including characteristics of duty and discipline. Coping also reflects cognitive features such as the ability to face and solve problems and to learn with experience. Finally, Anxiety is the reverse of Harmony, and Stability is how the system "flows" along time in terms of rhythm and predictability. These dimensions are called the Emotional traits for simplicity, although cognitive and motivational aspects are also covered. The examination of these traits has the advantage of providing an in-depth personalized and specific profile at the cost of easy communication.

The major patterns of "relationships between the parts" (emotional traits) are expressed as the Affective Temperaments. This global perspective derived from the five affective temperaments proposed by Akiskal based on Kraepelin's fundamental states [8]. However, we realized that there should be other common configurations, starting with the euthymic predisposition. Conceiving an orthogonal matrix of two major independent axes (Activation and Inhibition), each divided in high, medium, and low, the 3×3 possible combinations suggested the existence of nine types. We later realized that still other types were necessary to cover adequately the area of the matrix, for example, to differentiate the more extrovert but mostly stable hyperthymic type from the externalized and less adaptive euphoric type. The final classification of affective temperaments is as follows:

Internalized or Introvert Types

- Depressive or melancholic: tendency towards melancholy and sadness, takes little fun and joy in things, tends to put oneself down, quiet
- Anxious or avoidant: worrier, careful, often feels insecure and apprehensive, afraid that bad things will happen, avoids risky situations, always alert and vigilant
- Apathetic: has little initiative, often drifts away from what others are saying or doing, often fails to finish what has started, tends to be passive and slow

Unstable Types

- Cyclothymic: unpredictable and unstable mood, quick and disproportionate reactions, periods of high energy and enthusiasm alternate with other phases of sluggishness and loss of interest
- Dysphoric: tense and uneasy, with a strong tendency to feel agitated, anxious, and irritated at the same time
- Volatile: restless, disorganized, and easily distracted; sometimes hasty or inconvenient, quickly loses interest; often fails to do duties and to finish what has started

Stable Types

- Obsessive: dedicated, demanding, detail oriented, inflexible, and a perfectionist; needs to be in control of things; does not deal well with uncertainty and mistakes
- Euthymic: balanced and predictable, with mood changes only when there is a clear reason; usually in good spirits and feeling good about oneself
- Hyperthymic: always in good spirits, very confident, and has fun easily; loves novelties; active, obstinate, and with a tendency to leadership

Externalized or Extrovert Types

- Irritable: very frank, direct, and determined, but also angry, explosive, and suspicious
- Disinhibited: restless, active, spontaneous, and distracted; often rushes and acts carelessly; leave things to the last minute; when irritated, gets over it quickly
- Euphoric: expansive, fast, talkative, and intense; has many ideas and is easily distracted; hasty, explosive, and impatient; takes risks when overconfident or excited; overindulges in pleasurable things; does not like routines and rules

The AFECT Model, Mood Spectrum Disorders, and Borderline Personality Disorder

Mood is usually conceived as one dimension from sad/apathetic to happy/euphoric, and bipolar disorder is often described as the alternation between these states. These are simplistic and equivocal definitions that fail to address more complex presentations related to mood such as irritable, dysphoric, agitated, anxious, and worried states, which are indeed very common mixed features in subjects with bipolarity, in addition to euthymia.

The concept of mood spectrum has regained considerable attention in recent years, particularly due to the works of Akiskal and Angst. Angst has proposed a model that combines Major and minor mania (M and m) and depression (D and d) as independent from each other. The range of mood states from elevated to low mood goes in the following order: M, m, MD, Md, md, mD, d, D. This is a considerable conceptual advance compared to the previous lack of models or to the dichotomy of prototypical manic-depressive illness and major depression. However, Angst's model fails to explain (1) euthymia and how it can be "in between" mania and depression without being a mixed state; (2) how depression and mania can occur separately but also combined; (3) why some aspects cancel each other, e.g., being elated and depressed does not happen exactly at the same time, while other aspects do not cancel each other and acquire a different presentation (mixed states); (4) how mood oscillates between these states or tends to remain stable; and (5) other "energetic dysfunction" such as recklessness and hyperactivity without elation.

First, it is important to differentiate mood states (short-term presentations) from temperament traits (long-term tendencies), but to understand that temperament is the basis upon which mood is expressed according to internal and external stimuli. Both mood and traits can be understood using the same system principles. To gain insight into how various mood states and patterns emerge, we suggest that mood should be regarded as the *result* of the interaction between the emotional and cognitive traits within a context. This is depicted in Fig. 8.2, which shows the bidimensional matrix with euthymia in the center and altered mood states in the periphery (including attention deficit and hyperactivity). Also, Table 8.1 displays the general emotional/cognitive configurations of the 12 affective temperaments.

Euthymia (euthymic mood) results from a balanced expression of Activation as high Energy/Volition with low Desire and Anger, moderate Inhibition (more Caution than Fear), high Control and Coping, and low Sensitivity and Anxiety. This tends to high (mood) Stability and positive affectivity. Euthymic temperament is the predisposition to this configuration of emotions and cognitive functioning over time. Hyperthymic mood and temperament are similar, but with somewhat higher Activation and lower Inhibition, whereas the obsessive profile is slightly more inhibited, anxious, and angry, but still relatively stable over time. These three configurations are the stable types. The euthymic and hyperthymic types are protective against mental disorders.

The internalized types and moods (depression) have a dysregulation of Activation characterized by lower Volition/Energy and low to moderate Anger and Desire, along with high Inhibition. Control and Coping are low to moderate, and Anxiety and Sensitivity are moderate to high. The apathetic type tends towards particularly low Control and Coping, and the anxious type stands out for high Inhibition. The depressive mood and temperament has oversensitivity and low Volition as its hallmark features. All are relatively unstable overtime due to these dysfunctional emotional and cognitive expressions. These profiles commonly underlie internalized behaviors and disorders such as social avoidance and generalized anxiety.

The externalized types and moods (mania) also have some deficiencies in Coping and Control, but their excesses arise from increased Anger and Desire associated with low Inhibition. This mixture results in more Anxiety and low Stability. The disinhibited type particularly lacks Control and Caution, the irritable type displays excessive anger, and the euphoric type shares these two tendencies. These configurations also give rise to externalized behaviors such as drug abuse and excessive buying.

Finally, the unstable types and moods (dysphoria) are characterized by a combination of moderate to low Control and Coping along with high Sensitivity and Anxiety, Activation expressed mostly as Anger and Desire and Inhibition as more Fear than Caution. These features result in emotional reactivity and low Stability overtime. The volatile types have particularly low Control and Coping, whereas cyclothymics are more sensitive, angry, and impulsive (low Caution and high Desire).

The unstable temperaments predispose to behaviors and disorders of externalization, internalization, and executive function (such as ADHD). Also, the co-occurrence of emotional excesses and deficiencies along with poor Control and Coping leads to

Table 8.1 Emotional trait profiles of affected temperaments

	Volition	Desire	Anger	Fear	Caution	Sensitivity	Anxiety	Control	Coping	Stability
Depressive	↓↓	↓	↔	↑↑	↑↑	↑↑	↑↑	↓	↓↓	↓
Anxious	↔	↓	↔	↑↑	↑↑	↑	↑	↑	↓	↔
Apathetic	↓	↓	↓	↑	↑	↑	↔	↓↓	↓↓	↔
Cyclothymic	↔	↑↑	↑↑	↔	↓	↑↑	↑↑	↔	↓	↓↓
Dysphoric	↔	↑	↑↑	↔	↔	↑	↑↑	↔	↓	↓↓
Volatile	↓	↑	↑	↔	↓	↑	↑	↓↓	↓↓	↓↓
Obsessive	↑	↔	↑	↔	↑↑	↔	↔	↑↑	↑	↔
Euthymic	↑↑	↓↓	↓↓	↓	↑↑	↓↓	↓↓	↑↑	↑↑	↑↑
Hyperthymic	↑↑	↔	↓	↓↓	↑	↓↓	↓↓	↑↑	↑↑	↑
Irritable	↑	↑	↑↑	↓	↔	↔	↔	↑	↑	↓
Disinhibited	↑	↑↑	↔	↓	↓	↔	↔	↓	↔	↓
Euphoric	↑	↑↑	↑↑	↓↓	↓↓	↔	↑	↔	↑	↓↓

↓↓ very low, ↓ low, ↔ moderate, ↑ high, ↑↑ very high

Table 8.2 BPD features related to traits of the AFECT model

BPD features	AFECT model traits
Idealization and devaluation	↑ Desire (expectations), ↑ Anger ("all or nothing" pattern)
Interpersonal sensitivity	↑ Sensitivity, ↓ Coping
Impulsive and reckless behaviors	↓ Caution, ↓ Control, ↑ Desire
Self-harm and suicidal attempts	↑ Anger, ↑ Sensitivity, ↓ Volition
Difficulty maintaining actions with no immediate reward	↓ Volition, ↓ Control, ↑Desire
Attention deficits	↓ Control
Emptiness	↓ Volition
Victimization	↓ Coping
Unstable self-image, relationships, and sense of identity	Linked to ↓ Stability resulting from interaction between other traits
Typical emergence in adolescence	When Desire and Anger ↑, but self-regulatory traits (Coping, Control, and Caution) not yet mature
Long-term improvement during adulthood	Self-regulatory traits mature and "hot emotions" (Desire and Anger) attenuate

high tension and desperation, which may manifest as psychosomatic disorders, panic, compensatory behaviors to frustration (e.g., binge eating or drinking), and inward aggression (e.g., self-mutilation). This configuration reflects the phenotype described as a borderline personality disorder (BPD) or borderline traits.

The symptoms of BPD can be interpreted in the light of the emotional and cognitive traits. The overall picture is that emotional traits (Anger, Desire, Fear, Sensitivity) overwhelm the self-regulatory abilities of cognitive traits (Control, Coping, and Caution). Specific features of BPD related to traits are interpreted in Table 8.2.

AFECTS: A Short Self-Report Scale to Assess Emotional Traits and Affective Temperaments

Using the Internet to provide good sampling (the Brazilian Internet Study on Temperament and Psychopathology – BRAINSTEP) [9], we developed the AFECTS (see the full revised version in the Appendix), which evolved from a preliminary version called the Combined Emotional and Affective Temperaments Scale (CEATS) [10]. The AFECTS emotional section was composed of bipolar items, 5 of them with 8 items and 5 with 4 items (when the dimension of Inhibition is split into Fear and Caution, which "behave" differently depending on the kind of analysis performed). The original version [1] and the revised version [11] showed good or very good internal consistency in all dimensions and worked well in confirmatory analysis.

The Affective Section is composed of 12 short descriptions rated in a 5-point Likert scale (scored 1–5 from "nothing like me" to "exactly like with me.") followed by a question to choose the most precise description of the subject's temperament. This allows both a dimensional and a categorical evaluation of affective temperaments. Importantly, 99 % of subjects rated at least one affective temperament as a score 4 or 5, suggesting that all major patterns were covered [1]. However, ~30 % of subjects considered that only one description was a perfect match (score 5), and about 80 % considered that 1–3 descriptions of affective temperaments were compatible with their profile, usually with types within the same group (e.g., someone who chooses the cyclothymic temperament could also have a high score in dysphoric and volatile) or in "neighbor" types (e.g., volatile and apathetic, hyperthymic and euphoric) according to the matrix (Fig. 8.2).

Studies Using the AFECTS

Five studies have now been published with the AFECTS (without Anxiety and Stability dimensions) using data from the BRAINSTEP project. Overall, they show that the AFECTS is very sensitive to detect differences between groups and reveals specific patterns according to the independent variables tested.

The studies on bullying [12] and cocaine use [13] are of particular relevance to mood spectrum disorders and BPD [14]. Bullying was evaluated according to time exposed to bullying behavior (e.g., none, less than 1 year, from 1 to 3 years, and over 3 years) and cocaine use (e.g., no use, low use, abuse, and dependence) using the ASSIST scale [15].

The first important observation regarding emotional traits is that *all* dimensions varied significantly between groups, although some dimensions showed more pronounced differences than others. Bullying was particularly associated with higher Emotional Sensitivity and lower Volition, but also with higher Anger and lower Control and Coping. In contrast, higher cocaine involvement correlated with lower Caution, Coping, and Control and higher Anger and Desire. These patterns suggest that indeed the mind works as an integrated system, i.e., although some traits may be particularly associated with or affected by a particular type of event, there are "general" changes of lower magnitude in other dimensions. Since the AFECTS items include mood, motivation, basic emotions, behaviors, and cognition, these results reinforce the high degree of associative coherence between these dimensions. Such a phenomenon probably underlies the multiple "comorbidities" in psychiatric disorders.

It is also important to consider how the combination of traits may act synergistically or have opposing effects. For example, cocaine-dependent subjects showed very low scores on items of self-regulation (Control, Caution, and Coping) and very high scores in the externalizing emotions of Desire and Anger. This combination produces unrestrained impulses. It is relevant to point out that these are mean differences between groups. A specific cocaine-dependent subject may have only three

dimensions far from the "healthy" range (e.g., Control, Coping, and Desire). Another subject may have low Caution and high Desire and Anger, which facilitate cocaine experimentation, but fairly good Coping and Control that prevent the development of drug dependence. Of note, the temperament scores in those with very low cocaine use are in between dependents and controls, suggesting that these traits lead to cocaine experimentation since the sporadic use is unlikely to produce changes in temperament.

Different circadian profiles were also related to emotional and affective traits [16]. The Circadian Energy Scale assesses the energy level in the morning and evening and provides a general index and categorization of morningness-eveningness. Volition/Energy, Coping, and Control were positively correlated with high and stable Energy, contrary to Sensitivity. Control, Energy, Caution, and Coping were particularly low in evening types and high in morning types. Cyclothymic, volatile, depressive, and apathetic types have particularly low energy in the morning, whereas hyperthymic, disinhibited, and euphoric types have very high energy in the evening. Cyclothymics, volatiles, and euphorics have the highest difference between morning and evening energy.

The relationship between affective temperaments and defensive styles using the Defensive Style Questionnaire (DSQ-40) was also studied [17]. Hyperthymic or euthymic temperaments were more likely to present a mature defense style, whereas immature styles were predominant among individuals with cyclothymic, volatile, depressive, dysphoric, euphoric, and disinhibited temperaments. Higher immature and lower mature defense style scores were independently associated with depressive symptoms. As expected, euthymic or hyperthymic temperaments endorsed less depressive symptoms. Of note, euthymic and hyperthymic temperaments moderated the correlations of mature/immature defense and depressive symptoms.

The most recent work evaluated how the development of bodily symptoms (evaluated with the Somatization score of the SCL-90) relates to affective temperaments and defense mechanisms [18]. The results showed high somatic symptom severity in those with dysphoric, cyclothymic, and depressive temperaments and those who adopted displacement, somatization, and passive aggression as their predominant defense mechanisms presented. Individuals with dysphoric temperament and higher displacement scores were more likely to present bodily symptoms after controlling for age, gender, education, and depressive symptoms. Also, the relationship of dysphoric temperament with somatic symptom severity was much more powerful in people who adopted displacement as their predominant defense.

Altogether, these studies suggest that somewhat specific dysfunctional configurations of emotional traits and some affective temperaments are related to maladaptive behaviors and symptoms (cocaine abuse, somatic pain, depressive symptoms, and low morningness). Also, being a victim of bullying may have a widespread deleterious effect on temperament. However, these conclusions should be taken cautiously, as the results are derived from cross-sectional studies and therefore do not establish cause-effect relationships.

The AFECTS in Subjects with Borderline Personality Disorder, Bipolar Disorder, and Depression

Using the BRAINSTEP data bank [9] on 25,740 subjects, we selected the 290 subjects who have received a BPD diagnosis (20.7 % males, age 28.8 ± 8.3 years) and compared to the first 290 individuals who received a diagnosis of major depression (24.7 % males, age 29.2 ± 9.3 years), 290 subjects with a diagnosis of bipolar disorder (26.4 % males, age 28.9 ± 9.2 years), and 290 controls (32.3 % males, age 29.2 ± 9.3 years) who stated not ever having had a psychiatric diagnosis.

The emotional profile of these subjects (mean ±95 % CI adjusting for age and sex using multivariate analysis of covariance with Bonferroni confidence interval adjustment) is shown in Fig. 8.3. As can be seen, except for Fear, all traits differentiated patients from controls. The common characteristics of the three disorders are low Volition and Coping and high Anxiety. BPD subjects stand out for very high Anger and Desire and low Coping and Stability. Overall, subjects with bipolar disorder have a similar profile but with slightly less pronounced differences from controls, and only Anger was statistically different from BPD subjects. Those with a diagnosis of depression had lower Anger and Desire and higher Control, Caution, and Stability than BPD subjects but were still different from control subjects. Only subjects with depression showed significantly more Fear than controls.

Figure 8.4 shows the distribution of affective temperaments in these groups. As expected, most controls had stable affective temperaments, but were also frequently

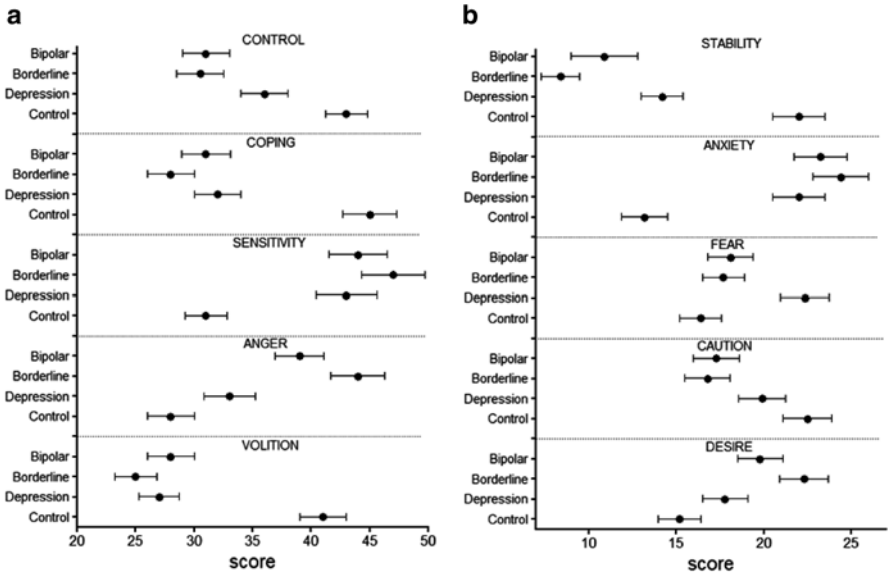

Fig. 8.3 Emotional profile of categorical affective temperaments. Data are shown as mean ± 95 % confidence interval

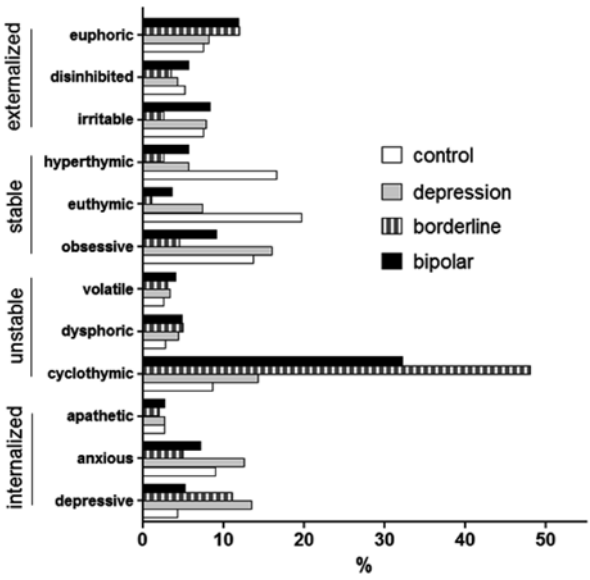

Fig. 8.4 Distribution of categorical affective temperaments in those with a diagnosis of major depression, bipolar disorder or BPD, and controls. $n = 290$ for each group

anxious, irritable, or euphoric. Those with a diagnosis of depression were mostly in the depressive, anxious, cyclothymic, and obsessive categories. BPD and bipolar subjects were more frequently cyclothymic and euphoric, and BPD individuals were nearly absent among euthymics and hyperthymics.

Altogether, these results suggest substantial similarities in the temperament of BPD and bipolar individuals, but some dysfunctional traits are slightly more pronounced in BPD subjects. The combination of high externalizing emotions (Desire, Anger), low self-regulating traits (Control, Coping, and Caution), low Volition, and high Sensitivity and Anxiety suggests a general emotional and cognitive dysregulation associated with these disorders. In our view, mood is influenced by all these traits in a given context. Therefore, therapeutic interventions should take into account all these traits. Research on how pharmacological and psychotherapeutic treatments tackle these traits is warranted.

Perspectives

Our line of research has two new directions. One focuses on the causes of dysfunctional traits, with particular emphasis on the effect of different types of trauma and deprivation, as well as their duration and timing during development. The second line is the development of a personality model based on the AFECT model addressing relationships (familial, friends, colleagues, community members) and society and intellectual and existential values. We believe this stratification will help differentiate clinical presentations of BPD and bipolar disorders, since BPD affects

heavily the "layers" of family relationships and intimacy issues, whereas bipolarity may be more associated with the mental aspects related to society, intellect, and existence/spirit. This is apparent in the common thought content of mania, such as the will to save the poor and to change the world and the beliefs of having special powers and talents and being directly connected to God.

Final Considerations

In our view, a personalized diagnostic approach at the trait level is essential to recognize the strengths and weakness of individuals with or without a mental disorder. If the assumption that dysfunctional traits lead to mental disorders is correct, using a framework such as the AFECT model may help plan effective treatment strategies to most psychiatric disorders using a unified approach. In contrast, the current categorized entities classified in diagnostic manuals prompt the development of several "specific" treatments, but real-world experience and research data show that a single treatment (e.g., SSRIs) may be partially effective in many disorders. Also, the failure to identify and attenuate dysfunctional traits may contribute to recurrence and residual symptoms of chronic disorders.

The distinction between mood, behavior, emotions, and cognitions is tempting didactically and can be useful therapeutically, but these dimensions tend to be linked in associative coherence. Thus, the understanding of the mind as an integrated system may shed light into how it is organized, how specific events (e.g., childhood trauma) may disarrange the system as a whole, and how it can be improved by therapeutic interventions.

Appendix: AFECTS, Temperament Scale

1. **Emotional traits section**—Check the option (score from 1 to 7) that most accurately corresponds to *the way you are and act in general*. Each item has opposite characteristics, in which the score 4 is neutral between these opposites. There are no right or wrong answers. Answer according to what you are and not to what you would like to be. Check only one option per line. See in the example someone who feels *quite secure* (*very secure* would be score 7, *very insecure* would be score 1).

Example Insecure	1	2	3	4	5	**6**	7	Secure	
Pessimistic	1	2	3	4	5	6	7	Optimistic	1
It's hard for me to feel pleasure	1	2	3	4	5	6	7	It's easy for me to feel pleasure	2
Sad and downcast	1	2	3	4	5	6	7	Happy and cheerful	3
I have low self-esteem	1	2	3	4	5	6	7	I have high self-esteem	4

(continued)

(continued)

Example Insecure	1	2	3	4	5	**6**	7	Secure	
I am indifferent to new activities	1	2	3	4	5	6	7	I get excited about new activities	5
Unmotivated and disinterested	1	2	3	4	5	6	7	Motivated and interested	6
I lack goals and will power	1	2	3	4	5	6	7	I have goals and will power	7
Dull and lacking energy	1	2	3	4	5	6	7	Active and energetic	8
Cool and collected	1	2	3	4	5	6	7	Hasty	9
Moderate	1	2	3	4	5	6	7	Intense, all-or-nothing	10
Flexible	1	2	3	4	5	6	7	Stubborn	11
Patient	1	2	3	4	5	6	7	Impatient	12
Calm	1	2	3	4	5	6	7	Irritable	13
Peaceful	1	2	3	4	5	6	7	Aggressive	14
Controlled	1	2	3	4	5	6	7	Explosive	15
Trusting	1	2	3	4	5	6	7	Suspicious	16
Daring	1	2	3	4	5	6	7	Fearful	17
Uninhibited and spontaneous	1	2	3	4	5	6	7	Inhibited	18
Carefree	1	2	3	4	5	6	7	Worrier	19
I react quickly in the face of danger	1	2	3	4	5	6	7	I freeze in the face of danger	20
Reckless	1	2	3	4	5	6	7	Cautious	21
Impulsive, I act before I think	1	2	3	4	5	6	7	I think before I act	22
Careless	1	2	3	4	5	6	7	Careful	23
I enjoy taking risks	1	2	3	4	5	6	7	I avoid taking risks	24
I rarely feel guilty	1	2	3	4	5	6	7	I blame myself easily	25
I deal with rejection well	1	2	3	4	5	6	7	I deal with rejection poorly	26
I deal with criticism well	1	2	3	4	5	6	7	I'm sensitive to criticism	27
I hardly ever get hurt emotionally	1	2	3	4	5	6	7	I easily get hurt emotionally	28
I find it easy to overcome traumas	1	2	3	4	5	6	7	I find it difficult to overcome traumas	29
I deal well with stress	1	2	3	4	5	6	7	I am sensitive to stress	30
I deal with pressure well	1	2	3	4	5	6	7	I perform poorly under pressure	31
I have a high tolerance for frustration	1	2	3	4	5	6	7	I have a low tolerance for frustration	32
I blame others for my mistakes	1	2	3	4	5	6	7	I take responsibility for my mistakes	33
I try to run away from my problems	1	2	3	4	5	6	7	I face my problems	34
I hope my problems solve themselves	1	2	3	4	5	6	7	I try to solve my problems	35
I let my personal problems pile up	1	2	3	4	5	6	7	I handle my personal problems as soon as I can	36
It is difficult for me to handle my conflicts with people	1	2	3	4	5	6	7	I easily handle my conflicts with people	37

(continued)

(continued)

Example Insecure	1	2	3	4	5	**6**	7	Secure	
I have trouble finding solutions	1	2	3	4	5	6	7	I find solutions easily	38
I tend to repeat my mistakes	1	2	3	4	5	6	7	I learn from my mistakes	39
Suffering has made me more fragile	1	2	3	4	5	6	7	Suffering has made me stronger	40
It is hard for me to pay attention	1	2	3	4	5	6	7	It is easy for me to pay attention	41
Distracted	1	2	3	4	5	6	7	Focused	42
I plan my activities poorly	1	2	3	4	5	6	7	I plan my activities well	43
I fail to finish tasks I have begun	1	2	3	4	5	6	**7**	I finish tasks, even when they are long and difficult	44
Disorganized	1	2	3	4	5	6	7	Organized	45
Undisciplined	1	2	3	4	5	6	7	Disciplined	46
Irresponsible	1	2	3	4	5	6	7	Responsible	47
Negligent	1	2	3	4	5	6	7	Perfectionist	48
My desires are weak	1	2	3	4	5	6	7	I have strong desires	49
I am tempered in terms of what I like	1	2	3	4	5	6	7	I indulge in what I like	50
I am able to resist temptations	1	2	3	4	5	6	7	I easily give in to temptations	51
I manage to control myself when I really want something	1	2	3	4	5	6	7	I can do “crazy” things when I really want something	52
In peace	1	2	3	4	5	6	7	Anxious	53
Relaxed	1	2	3	4	5	6	7	Tense	54
Serene	1	2	3	4	5	6	7	Apprehensive	55
I rarely feel troubled	1	2	3	4	5	6	7	I often feel troubled	56
Turbulent	1	2	3	4	5	6	7	Balanced	57
Unstable	1	2	3	4	5	6	7	Stable	58
Unpredictable	1	2	3	4	5	6	7	Predictable	59
Oscillating	1	2	3	4	5	6	7	Steady	60

Scoring: Volition (1–8), Anger (9–16), Fear (17–20), Caution (21–24), Emotional Sensitivity (25–32), Coping (33–40), Control (41–48), Desire (49–52), Anxiety (53–56), Stability (57–60)

2. **Affective Temperament section**—For each description below, please check the alternative that best corresponds to you (check only one alternative).

   (A) I have a tendency towards melancholy and sadness; I see little fun and joy in things; I tend to put myself down; I don’t like changes; I prefer to listen than to talk.

Nothing like me	☐ ☐ ☐ ☐ ☐	**Exactly like me**

(B) I am a big worrier and very careful; I often feel insecure and apprehensive; I am afraid that bad things will happen; I try to avoid risky situations; I am always alert and vigilant.

Nothing like me	☐ ☐ ☐ ☐ ☐	**Exactly like me**

(C) I have little initiative; I often drift away from what others are saying or doing; I often fail to finish what I have started; I tend to be passive and a bit slow.

Nothing like me	☐ ☐ ☐ ☐ ☐	**Exactly like me**

(D) My mood is unpredictable and unstable (highs and lows), changes quickly or in a way that is disproportionate to the facts; I have periods of high energy, enthusiasm, and agility that alternate with other phases of sluggishness, loss of interest, and discouragement.

Nothing like me	☐ ☐ ☐ ☐ ☐	**Exactly like me**

(E) I am tense and uneasy, with a strong tendency to feel agitated, anxious, and irritated at the same time.

Nothing like me	☐ ☐ ☐ ☐ ☐	**Exactly like me**

(F) I am restless, disorganized, and easily distracted; sometimes I am hasty or inconvenient and only realize it when it is too late; I quickly lose interest; I often fail to do what I should and finish what I have started.

Nothing like me	☐ ☐ ☐ ☐ ☐	**Exactly like me**

(G) I'm dedicated, demanding, detail oriented, inflexible, and a perfectionist; I need to be in control of things; I don't deal well with uncertainty and mistakes.

Nothing like me	☐ ☐ ☐ ☐ ☐	**Exactly like me**

(H) My mood is balanced and predictable; I usually have mood changes only when there is a clear reason; I am usually in good spirits; and, in general, I feel good about myself.

Nothing like me	☐ ☐ ☐ ☐ ☐	**Exactly like me**

(I) I am always in good spirits; I am very confident and I have fun easily; I love novelties; I do many things without getting tired; I pursue what I want until I get it; I have a strong tendency to leadership.

Nothing like me	☐ ☐ ☐ ☐ ☐	**Exactly like me**

(J) I'm very frank, direct, and determined, but also angry, explosive, and suspicious.

Nothing like me	☐ ☐ ☐ ☐ ☐	**Exactly like me**

(K) I am restless, active, spontaneous, and distracted; I often rush and act carelessly; it is very common for me to leave things to the last minute; when I get irritated, I get over it quickly.

Nothing like me	☐ ☐ ☐ ☐ ☐	**Exactly like me**

(L) I am expansive, fast, talkative, and intense; I have many ideas and I am easily distracted; I am hasty, explosive, and impatient; I take risks when overconfident or excited; I overindulge in things I enjoy; I do not like routines and rules.

Nothing like me	☐ ☐ ☐ ☐ ☐	**Exactly like me**

3. **Choose the description** (**from A to K**) **from question 2 above that best describes you** (***only one alternative***). Please read carefully those that describe you best before choosing your answer.

A	B	C	D	E	F	G	H	I	J	K	L

Affective temperament types in order: (A) Depressive; (B) Anxious; (C) Apathetic; (D) Cyclothymic; (E) Dysphoric; (F) Volatile; (G) Obsessive; (H) Euthymic; (I) Hyperthymic; (J) Irritable; (K) Disinhibited; (L) Euphoric

References

1. Lara DR, Bisol LW, Brunstein MG, Reppold CT, de Carvalho HW, Ottoni GL. The Affective and Emotional Composite Temperament (AFECT) model and scale: a system-based integrative approach. J Affect Disord. 2012;140:14–37.
2. Cuthbert BN, Insel TR. Toward the future of psychiatric diagnosis: the seven pillars of RDoC. BMC Med. 2013;11:126.
3. Akiskal HS. Toward a definition of generalized anxiety disorder as an anxious temperament type. Acta Psychiatr Scand Suppl. 1998;393:66–73.

4. Cloninger CR, Svrakic DM. Personality disorders. In: Sadock BS, Sadock VA, editors. Kaplan and Sadock's comprehensive textbook of psychiatry. 7th ed. Philadelphia: Lippincott Williams &Wilkins; 2000. p. 1723–64.
5. Di Fiorino M, Martinucci M. The theory of humours. In: Di Fiorino M, editor. Figures of Melancholia and Mania – Forte dei Marmi. Bridging Eastern and Western Psychiatry; 2007. p. 493–5.
6. Lara DR. Os princípios da mente e da personalidade. Neurociências. 2010;5:212–8.
7. Walach H. The complementarity model of brain-body relationship. Med Hypotheses. 2005;65:380–8. doi:10.1016/j.mehy.2005.01.029. http://intl.elsevierhealth.com/journals/Doi10.1016/j.mehy.2005.01.029.
8. Kraepelin E. Manic depressive insanity. Edinburgh: Livingstone; 1921.
9. Lara DR, Ottoni GL, Brunstein MG, Frozi J, de Carvalho HW, Bisol LW. Development and validity data of the Brazilian Internet Study on Temperament and Psychopathology (BRAINSTEP). J Affect Disord. 2012;141:390–8.
10. Lara DR, Lorenzi TM, Borba DL, Silveira LC, Reppold CT. Development and validation of the Combined Emotional and Affective Temperament Scale (CEATS): towards a brief self-rated instrument. J Affect Disord. 2008;111:320–33.
11. Carvalho HW, Lara DR. Towards an integrative model for the comprehension of psychopathology. In: 3rd International Congress on Neurobiology, Psychopharmacology and Treatment Guidance. 2013; Thessaloniki, Greece.
12. Frizzo MN, Bisol LW. Lara DR Bullying victimization is associated with dysfunctional emotional traits and affective temperaments. J Affect Disord. 2013;148:48–52.
13. Fuscaldo LV, Bisol LW, Lara DR. How emotional traits and affective temperaments relate to cocaine experimentation, abuse and dependence in a large sample. Addict Behav. 2013;38:1859–64.
14. Wolke D, Schreier A, Zanarini MC, Winsper C. Bullied by peers in childhood and borderline personality symptoms at 11 years of age: a prospective study. J Child Psychol Psychiatry. 2012;53(8):846–55. doi:10.1111/j.1469-7610.2012.02542.x.
15. WHO ASSIST Working Group. The Society for the Study of Addiction to Alcohol and Other Drugs. The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST): development, reliability and feasibility. Addiction. 2002;97:1183–94.
16. Ottoni GL, Antoniolli E, Lara DR. Circadian preference is associated with emotional and affective temperaments. Chronobiol Int. 2012;29:786–93.
17. Carvalho AF, Hyphantis TN, Taunay TC, Macêdo DS, Floros GD, Ottoni GL, Fountoulakis KN, Lara DR. The relationship between affective temperaments, defensive styles and depressive symptoms in a large sample. J Affect Disord. 2013;146:58–65.
18. Hyphantis TN, Taunay TC, Macedo DS, Soeiro-de-Souza MG, Bisol LW, Fountoulakis KN, Lara DR, Carvalho AF. Affective temperaments and ego defense mechanisms associated with somatic symptom severity in a large sample. J Affect Disord. 2013. doi:10.1016/j.jad.2013.04.043. pii: S0165-0327(13)00344-3.

Part IV
Developmental Features and Longitudinal Course

Chapter 9
Borderline Personality and Mood Disorders: Risk Factors, Precursors, and Early Signs in Childhood and Youth

Andrew M. Chanen and Katherine Thompson

Introduction

Approximately 75 % of all mental disorders have their onset by the age of 25 years, with the peak period of onset for the major mental disorders, including depression, bipolar disorder, and borderline personality disorder, occurring in the period from puberty through to young adulthood [1–5].

However, mental disorders do not present autochthonously. Young people most commonly present with an evolving mixture of symptoms, and our limited understanding of the prospective relationships between these symptoms and the major mental disorder syndromes suggests a more complicated picture. Diagnostic clarity is often only possible in retrospect. Nonetheless, even without a clear diagnosis, the presence of psychopathology and distress can have adverse consequences upon development, such as disruption to education, work, and relationships with family and peers. This is particularly the case when treatment is delayed [2, 6], which can lead to persistent functional deficits.

On this basis, there is a clear need for effective early intervention. This term defines both early detection and intervention for subsyndromal (a.k.a. indicated prevention) and syndromal (first episode) mental disorders to reduce the burden of

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disease among young people and their families. One key challenge for early intervention is to balance the sensitivity and specificity of any early detection program. Effective early intervention improves the developmental and functional outcomes for individuals. Spurious diagnostic certainty can lead to the misapplication of diagnostic labels, stigma, inappropriate treatment, and other adverse outcomes.

The debate about the relationship between borderline personality disorder and the mood disorders has largely been framed around the phenomenology of the respective disorders, rather than their etiology or pathogenesis [7]. Most phenomenological studies have been conducted in adults, when the disorders have largely "run their course" and where retrospective reports are often hampered by recall bias, making uncertain the timing of symptom and/or disorder onset [2]. Moreover, the use of patient samples in many studies [8, 9] means that "Berkson's bias" [10], whereby people who meet criteria for multiple disorders are more likely to be treatment seeking than people who meet criteria for just one disorder, is likely to lead to inflated levels of co-occurrence.

Clinical assessment tends to focus upon eliciting risk factors and phenomenology from the patient's life narrative. This chapter focuses upon the challenge of early intervention for borderline personality and mood disorders in the real-world clinical context of phenomenological change and evolution and where many risk factors (particularly environmental factors) commonly lead to diverse outcomes (i.e., multifinality) [11]. It therefore draws upon prospective, longitudinal data (where available) regarding the development of these disorders and proposes a pragmatic heuristic framework for conducting early intervention.

Risk Factors, Precursors, and Early Signs of Psychopathology in Young People

Borderline Personality Disorder

Despite long-standing general agreement that personality disorders have their roots in childhood and adolescence [12], diagnosing personality disorders prior to age 18 years has been more controversial than diagnosing personality disorders in adults [13], but this is no longer justified [14, 15]. Borderline personality disorder is increasingly seen as a lifespan developmental disorder [16] that is similarly reliable and valid when applied to adolescents or adults [17, 18], is not reducible to other diagnoses [19], and can be identified in day-to-day clinical practice [20].

In fact, borderline personality disorder might be better considered as a disorder of younger people, with a rise in prevalence from puberty and a steady decline with each decade from young adulthood [21–23]. Limited data suggest that borderline personality disorder occurs in approximately 3 % of community dwelling [24, 25] and up to 22 % of outpatient [20, 26] adolescents and young adults.

Borderline personality disorder (or dimensional representations of borderline personality disorder) in young people demarcates a group with high morbidity and

a particularly poor outcome. Borderline personality disorder uniquely and independently predicts current psychopathology, poor general functioning, poor self-care, and poor relationships with family, peers, and significant others [19, 27]. It also uniquely predicts poor outcomes up to two decades into the future, such as a future borderline personality disorder diagnosis, increased risk for other mental disorders (especially substance use and mood disorders), interpersonal problems, distress, and reduced quality of life [4, 28, 29].

There is now clear evidence that dimensional representations of borderline personality disorder features have similar stability in adolescence and adulthood [17]. Evidence is emerging that the underlying dimensions of borderline personality disorder features (conceptualized as impulsivity, negative affectivity, and interpersonal aggression) might also be relatively stable in children [30, 31]. Only one study has specifically measured childhood or adolescent personality disorder features as a predictor of later personality disorder over multiple assessments from childhood to adulthood [4]. Personality disorder symptoms in childhood or adolescence were the strongest long-term predictors, over and above disruptive behavior disorders and depressive symptoms [4, 32–34], of later DSM-IV cluster A, B, or C personality disorder. Overall, these data support a normative increase in borderline personality disorder traits after puberty, perhaps bringing the problems associated with borderline personality disorder to clinical attention. As this wanes in early adulthood, partly due to maturational or socialization processes [4], a group is revealed that is increasingly deviant compared with their peers [35] and perhaps conforms more to the "adult" borderline personality disorder phenotype. This suggests that young people displaying borderline personality disorder features are the major group from which the adult borderline personality disorder phenotype arises.

Heritability estimates for borderline personality disorder (or dimensional representations of borderline personality disorder) range from 35 to 45 % [36]. Experiences of childhood abuse or neglect, problematic family environment, as well as low socioeconomic status are significant risk factors for the development of personality pathology and specifically borderline personality disorder [36]. Prospective, longitudinal data also indicate that certain temperamental characteristics and early-onset mental state or behavioral problems that are analogous to characteristics of borderline personality disorder are precursors to the emergence of the borderline personality disorder phenotype, but do not predict its onset with certainty. However, it is technically imprecise to refer to many of these phenomena as "risk factors" [37], as these same phenomena are later used to define borderline personality disorder. Rather, they are better termed *precursor signs and symptoms* [38]. Typical phenomena include those of attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), conduct disorder (CD), substance use, depression, and deliberate self-harm (DSH), along with the actual features of borderline personality disorder [36].

For example, maternal reports of childhood temperament are related to borderline personality disorder in adolescence or adulthood, up to 30 years later [39, 40]. Substance use disorders during adolescence, particularly alcohol use disorders, also specifically predict young adult borderline personality disorder [41, 42], and strong

prospective data demonstrates that disturbances in attention, emotional regulation, and behavior, especially the disruptive behavior disorders (CD, ODD, ADHD) in childhood or adolescence, are independent predictors of young adult borderline personality disorder [40, 43, 44]. Moreover, one study suggests that difficulties with emotion regulation and relationships might precede problems with impulse control in the development of adolescent borderline personality disorder [43].

Deliberate self-harm (DSH) is a core feature of borderline personality disorder [45], and retrospective reports from adults with borderline personality disorder indicate childhood onset of DSH in more than 30 % and adolescent onset in another 30 % [46]. However, DSH is surprisingly under-researched as a potential precursor to borderline personality disorder. Although DSH is relatively common among adolescents and young adults [47] and is associated with a range of clinical syndromes, there is evidence that repetitive DSH, which is less frequent, might differ from occasional DSH [48]. Borderline personality disorder can be diagnosed in the majority of female adolescent inpatients with DSH [49], and the likelihood of meeting the diagnosis of borderline personality disorder is greater in adolescents endorsing both DSH and suicide attempts compared with individuals reporting DSH or suicide attempts alone [50]. Also, the number of borderline personality disorder criteria met is predictive of whether or not an adolescent has engaged in DSH or attempted suicide [51].

The above findings are important because they provide evidence that the features of borderline personality disorder can be reliably and validly detected from at least the pubertal period onwards. However, borderline personality disorder features are often preceded by, accompany, or follow signs and symptoms that are also associated with other mental state disorders (so-called comorbidity), such as mood, anxiety, disruptive behavior, eating, and substance use disorders [19, 27, 52]. Taken together, these signs and symptoms appear from childhood through to adolescence. Many of these resemble aspects of the borderline personality disorder phenotype and presage its later appearance in adolescence or emerging adulthood. However, these factors have limited specificity for borderline personality disorder or other "adult" syndromes.

Bipolar Disorder

Similar to borderline personality disorder, the call for prevention and early intervention for bipolar disorder stems from concern over the consequences of diagnostic and treatment delay [53]. Approximately 70 % of individuals with bipolar disorder will experience their first symptoms before age 25, but there is often a considerable delay before a formal diagnosis is made [54]. Just over half of patients have been reported to be diagnosed in the first year of illness, but a diagnosis can take on average 8 years following the first episode [55, 56]. Also, there is often substantial delay between the onset of bipolar disorder and the introduction of mood-stabilizing medication. Delayed treatment can be linked with adverse outcomes, such as poor psychosocial

adjustment, increased hospitalization and suicide rates, substance use, forensic problems, and failure to achieve developmental milestones [55]. Taken together with evidence that mood stabilizers might have neuroprotective effects that prevent the structural brain changes associated with bipolar disorder, there is a clear rationale for early intervention in this patient group [53].

Children of parents with bipolar disorder are more likely to develop a range of mental disorders, especially affective disorders [57, 58]. Importantly, among the factors that confer an increased risk for a later diagnosis of bipolar disorder are many of the factors associated with borderline personality disorder. These include childhood or familial ADHD [59, 60], traumatic or stressful life events, childhood abuse [58, 61, 62], and substance abuse [63]. Even certain personality traits, such as high harm avoidance and high novelty seeking [64], along with impulsive aggression [58], are associated with later bipolar disorder.

A recent review from our group found 13 retrospective and 12 prospective studies of the period prior to the onset of first-episode mania [56]. Both prospective and retrospective studies highlight that the initial polarity of first illness presentation is more commonly depressive [55]. Retrospective studies have highlighted features such as sub-threshold mania, anger and irritability, lack of sleep, grandiosity, periods of depression, and, to a lesser extent, mood changes. Prospective studies have identified symptoms such as racing thoughts, irritability, anger, periods of depression, mood swings, anxiety, and in some cases psychotic symptoms [56, 65, 66]. The period of prodrome reported in these studies varies widely, from weeks to 15 years. This is in part due to study design, as studies that used samples "enriched" for risk of bipolar disorder reported a shorter time to transition than general samples.

The largest and most rigorous study to examine the incidence of hypomanic and depressive symptoms prospectively from adolescence through to adulthood [67] drew a random representative sample of 14-24 year-olds living in Munich, Germany. After baseline assessment, participants were assessed on 3 occasions over a 7.4–10.6-year period. The findings indicate that it was common for young people to experience hypomanic and depressive symptoms once (almost 40 % of 1,565 participants) over the follow-up period. However, it was far less likely for these symptoms to be experienced multiple times. The persistence of symptoms was more predictive of transition to clinically relevant outcomes (i.e., hypomanic or manic episodes or accessing mental health care) in a dose-dependent manner. The authors conclude that a nonclinical bipolar phenotype might be developmentally common and usually transitory during adolescence. The onset of clinical bipolar disorder is comparatively rare and might be seen as the poor outcome of these developmental processes.

The Course and Outcome of Bipolar Youth (COBY) study prospectively followed 413 7-17 year-olds with "bipolar spectrum" (bipolar I, II, or NOS) disorder over a period of 4 years [68]. This study specifically measured affective phenomena, including mania and depression, but it did not investigate the presence of other disorders. The findings indicate that mixed/cycling and depressive symptoms accounted for the greatest proportion of symptomatology. Rapid mood changes were frequently found, and almost all chronic symptoms reported were of the subsyndromal depressive type. The authors highlight that early onset confers greater likelihood of a chronic

and fluctuating course. While the authors argue that their results support the existence of brief episodes of manic or hypomanic symptoms that are clinically relevant, their failure to measure borderline personality disorder as an outcome or even salient phenomena associated with bipolar disorder renders this conclusion doubtful.

In response to a significant increase in the tendency to diagnose children and young people with bipolar disorder, Leibenluft [69] reviewed the evidence linking mood dysregulation, irritability, and bipolar disorder in young people. She argues that children who present clinically with non-episodic severe irritability are not manic. This is based on diagnostic studies of youth with severe mood dysregulation, where 84 % were found to also meet criteria for lifetime ODD, 86 % lifetime ADHD, 58 % lifetime anxiety disorder, and 16 % lifetime major depressive disorder (MDD). As noted above, these might also be seen as precursor signs and symptoms of borderline personality disorder [36], which was not measured in the studies cited. Leibenluft [69] also concludes that longitudinal studies suggest that severe mood dysregulation does not lead to bipolar disorder but that irritability predicts adult unipolar depression and anxiety disorders. Further to this, young people with irritability do not have high familial rates of bipolar disorder and have a different pathophysiology from youths with bipolar disorder. This review suggests that irritability is a common symptom of childhood and adolescence that has been underresearched. Its clinical presence does not justify a diagnosis of bipolar disorder in young people, as there is no evidence that it leads to adult bipolar disorder. This review underscores that predicting bipolar disorder prospectively, based on specific symptoms, remains fraught.

The problem these studies highlight is that symptoms preceding the first episode of mania lack specificity and sensitivity. Depressive symptoms have high sensitivity but low specificity for bipolar disorder. In contrast, low-grade mood elevation is more specific, but it is not present in all young people who will develop bipolar disorder. In order to balance the need for sensitivity and specificity, a "close-in" strategy (combining known risk factors to "close in" on the target population) [70] was developed by Bechdolf and colleagues [56]. The validity of bipolar at-risk (BAR) criteria was evaluated in a retrospective medical file audit study of nonpsychotic young people aged 15–24 years presenting for intake assessment at a psychiatric service. A total of 173 intake assessments were examined in relation to the BAR criteria. A total of 22 patients met BAR criteria at intake. After a mean period of 265.5 days post intake, 22.7 % ($n=5$) of the BAR group had developed a diagnosis of bipolar disorder, compared with only 0.7 % ($n=1$) in the non-BAR group. The authors concluded that the BAR criteria have some predictive validity in the proximal prodrome of bipolar disorder, and these criteria are currently being tested in a prospective study [56].

Taken together, the above studies indicate that borderline personality disorder and bipolar disorder share numerous distal risk factors and precursor signs and symptoms. Even the presence of specific symptoms of bipolar disorder in childhood and adolescence does not strongly predict the development of bipolar disorder per se. Factors such as the number and frequency symptoms, along with other factors associated with genetic predisposition and environment risk, appear to combine

together to predispose an individual to go on to develop an affective disorder in general and bipolar disorder specifically. Strategies to identify young people at risk of developing bipolar disorder are being developed, but they require further investigation.

Unipolar Depression

The pubertal period is associated with a marked rise in the incidence of depressive symptoms, with 20 % of young people experiencing a diagnosable episode of depression before the age of 18 years [71]. In fact, half of all first episodes of depression occur during adolescence, with an average age of onset of 15 years [72]. Depression during this developmental period has also been associated with increased risk for subsequent episodes and more chronic course [73]. Similar to the other disorders discussed above, adolescent depression is associated with adverse long-term functional and psychiatric outcomes [74]. These include impairment in education, vocation, and interpersonal relationships, substance use, and suicide.

Retrospective studies have investigated the pathways to depression, including risk factors and diagnostic characteristics of people who developed their first episode of depression during adolescence. For example, in a study of 198 women with depression who attended primary care practices [75], those who had their first episode of depression before the age of 16 years were more likely to have attempted suicide, engaged in self-harm, had a history of alcohol abuse, been pregnant as a teenager, and to have had more pervasive personality dysfunction, problems with attention and hyperactivity, and poorer peer relationships. They were also more likely to have experienced poor parental care, physical abuse, interpersonal violence, and childhood sexual abuse.

Another study of 372 adults who were participating in two randomized medication trials for the treatment of depression [76] compared the characteristics of patients according to whether their first episode of depression occurred during childhood, adolescence, or adulthood. They reported that the group who had adolescent-onset depression was significantly more likely to meet criteria for a DSM-IV diagnosis of personality disorder, most commonly avoidant personality disorder, followed by borderline personality disorder. Interpretation of the findings from each of these studies needs to be tempered by the potential for recall bias.

A recent review identified "specific" risk factors for depression that have been associated with increased risk for youth depression in empirical investigations, along with "nonspecific" risk factors that increase risk for a range of disorders, including depression [74]. Specific risk factors included low self-esteem, being female, having a negative body image, poor social support, and ineffective coping, together with having a parent with a depressive illness. However, the foundations for the claim of specificity are weak. For example, having a parent with a depressive illness is also associated with later bipolar disorder and anxiety disorder [58, 77].

Nonspecific risk factors included poverty, exposure to violence, social isolation, child maltreatment, and family breakdown. In contrast, protective factors included

supportive adults, strong family relationships, strong peer relationships, coping skills, and emotional regulation skills, focusing on age-appropriate developmental tasks, on relationships, and on understanding their parent's illness.

Individual differences in temperament, such as high negative emotionality, are also associated with vulnerability to depression and prospectively predict later depression [78]. Moreover, personality disorder and depression have been found to mutually reinforce one another over adolescence and young adulthood [4]. For example, borderline personality disorder traits, identified between ages 14 and 22, were significantly associated with risk for dysthymic disorder or major depressive disorder by a mean age of 33 after controlling for a history of unipolar depression and other psychiatric disorders [79].

Unsurprisingly, unipolar depression shares many distal risk factors and precursor signs and symptoms with borderline personality disorder and bipolar disorder. Depression is a common experience in adolescence, and the outcomes for young people with depressive symptoms might include depression, borderline personality disorder, or bipolar disorder but might also include good mental health. Importantly, the initial polarity of first illness presentation for bipolar disorder is more commonly depressive [55], making the clinical task of treatment initiation for the first presentation of depressive illness challenging.

"Comorbidity" in the Clinical Presentation of Borderline Personality Disorder

One of the pivotal problems when considering the diagnosis of borderline personality disorder is the high degree of co-occurring mental state and personality psychopathology. Empirical data suggest that the constructs of mental state disorders, personality traits, and personality disorders are substantially overlapping [80]. Among those with personality disorders, co-occurrence of mental state disorders and other personality disorders is common in both clinical and community settings. This is most striking for borderline personality disorder, where co-occurring mental state and personality disorders are the norm [81, 82]. In a nationally representative survey of adults (aged 18 years and older) in the United States, 84.5 % of those with borderline personality disorder met criteria for one or more mental state disorders in the past 12 months, with a mean of 3.2 mental state disorders [83]. Viewed from another perspective, 25.2 % of those with any mental state disorder in the previous 12 months also met criteria for at least one personality disorder. It is possible that, rather than being an artifact of the diagnostic system or an inconvenience, the tendency for mental disorders to co-occur might in fact be a predictable consequence of the involvement of common liability factors for multiple disorders [84].

This pattern of co-occurrence has been found to be similar in young people in community and clinical settings. In the Children in the Community study, the long-term prognoses for DSM-IV Axis I and Axis II disorders were of comparable magnitude and often additive when co-occurring [28]. Axis I (mood, anxiety, dis-

ruptive behavior, and substance use disorders) and Axis II disorders in adolescence showed risks for negative prognoses lasting 20 years. Co-occurring Axis I and Axis II disorders consistently presented the highest risk, at least the sum of the risk for each axis or even several times the risk of disorders in either axis alone.

In a clinical study comparing adolescent outpatients with borderline personality disorder, those with other personality disorders, and those with no personality disorder, those with borderline personality disorder had a significantly greater burden of co-occurring mood (59 %), anxiety (46 %), disruptive behavior (70 %), and substance use disorders (35 %) [19]. Similarly, in a sample of female adolescent inpatients with borderline personality disorder, the most frequent mental state disorders were mood (22 %), eating disorders (16 %), dissociative/somatoform (13 %), and substance use disorders (10 %) [27]. This pattern of co-occurrence in inpatients is similar to, but lower than, that found in adult samples. In this sample, 38.7 % of patients had one or more co-occurring personality disorders. The most common were cluster C (avoidant, dependent, obsessive-compulsive), followed by Cluster A (paranoid) [27]. Taken together, these studies show that the clinical presentation of borderline personality disorder is often associated with the presence of affective symptoms and other psycho-pathology.

The Relationship Between Borderline Personality Disorder and Mood Disorders

The prominence of affective criteria in the DSM diagnosis of borderline personality disorder and the significant co-occurrence of affective disorders (including bipolar I, bipolar II, major depression, and dysthymic disorder) in patients who have borderline personality disorder have fueled debate about whether borderline personality disorder should be conceptualized as a mood disorder [85]. It is beyond the scope of this chapter to review this literature, which has mainly been conducted in adults and which will be covered elsewhere in this book. Rather, relevant literature pertaining to these issues in young people will be covered.

Borderline Personality Disorder and Bipolar Disorder

Bipolar disorder and borderline personality disorder might be confused clinically because of the diagnostic criteria themselves. Many of the criteria for borderline personality disorder and bipolar disorder in the DSM-IV and its predecessors are related to mood instability [86]. Paris, Gunderson, and Weinberg [85] comprehensively explored the hypothesis that borderline personality disorder was in fact a bipolar spectrum disorder and argued that, more often than not, borderline personality disorder remains distinct from bipolar disorders cross-sectionally and over time. However, Barroilhet and colleagues have argued that the clinical debate about

overlap is scientifically false because the "core" features of mood lability and impulsivity are not central to either disorder [87]. They argue that bipolar disorder is primarily a disorder of psychomotor activation and that the borderline personality disorder criteria of abandonment, identity disturbance, recurrent suicidal or self-mutilating behavior, and dissociative symptoms distinguish borderline personality disorder from bipolar disorder.

Other authors have pointed to the importance of the nature of affect, which has a different time course and quality in borderline personality disorder compared with bipolar disorder. In contrast to the slower time course of affective change in bipolar disorder, borderline personality disorder affect is subject to rapid and chaotic changes over minutes, hours, or days [88], more commonly shifts between euthymia and anger [89], and is often triggered by environmental (especially interpersonal) factors [88].

While the hypothesis that borderline personality disorder is a bipolar disorder spectrum disorder is based largely on the observation of unstable mood, there is little research to support this idea [7]. One study sought to address the difficulty of differentiating between early bipolar disorder and borderline personality disorder in 87 depressed young people recruited from consecutive referrals to a psychiatric clinic [90]. The study aimed to measure borderline personality disorder pathology during an index depressive episode and to compare three diagnostic groups: bipolar disorder ($n=14$), "bipolar spectrum disorder" ($n=27$), and MDD ($n=46$). No participant met full diagnostic criteria for a personality disorder. Both of the bipolar-depressed groups reported significantly higher median levels of borderline characteristics than the MDD group. Three of the borderline characteristics emerged as potentially useful in differentiating bipolar depression from unipolar depression: "I've never threatened suicide or injured myself on purpose," "I have tantrums or angry outbursts," and "Giving in to some of my urges gets me into trouble." They conclude that certain borderline personality disorder screening questions that reflect cyclothymic characteristics or depressive mixed states might be of practical use to clinicians in helping to differentiate between bipolar depression and unipolar depression in young adults and that borderline personality disorder in early-onset depression is predictive of ultimate bipolar outcome. Among the major limitations to this study are the reliance on the screening questionnaire of the International Personality Disorders Examination, which does not perform well in young outpatients [20], the absence of any case level borderline personality disorder, and the fact that the diagnostic criteria for "bipolar spectrum disorder" are not validated.

Another study [91] investigated young people and young adults with early onset of bipolar disorder. They found that among this sample of 100 young people aged 15–36 years, greater comorbidity increased the risk of self-harm and suicide. A comorbid diagnosis of borderline personality disorder significantly increased the risk for self-harm but not suicide attempts. The most important finding from this study was that early onset of bipolar disorder was associated with the highest risk of self-harm and suicide attempts. This is supported by evidence that anxiety, concentration difficulties, antisocial behavior, and substance use are present in the early stages of bipolar disorder and correlate with an unfavorable course [92, 93].

These studies suggest that care needs to be taken to use all available diagnostic data when making a clinical assessment. Current research findings in young people are of limited direct application to everyday clinical practice. It is important to recognize that it is the nature and context of mood regulation difficulties that are paramount in distinguishing these disorders and that certain characteristics might aid this such as psychomotor activation or mood elevation for bipolar disorder, or abandonment, identity disturbance, recurrent suicidal or self-mutilating behavior, and dissociative symptoms for borderline personality disorder. Co-occurrence of bipolar disorder and borderline personality disorder is possible and appears to heighten the risk of self-harm or suicide.

Borderline Personality Disorder and Depression

The high prevalence of co-occurring depressive symptoms in young patients with borderline personality disorder [19] can potentially mask the presence of a personality disorder. In fact, borderline personality disorder and major depressive disorder are the only two disorders in the DSM-5 that include suicidal ideation or attempts in their diagnostic criteria. Although a great deal of research has been conducted on the subject of borderline personality disorder and depression in adults [94] and is covered elsewhere in this book, it is unclear how these findings apply to young people. This topic has received comparatively little attention in young people, especially in clinically applied research. It seems that the primary task is to encourage clinicians to even consider a diagnosis of borderline personality disorder in a young person presenting with depression. Clinical experience suggests that a common reason for not making a borderline personality disorder diagnosis in young people is that appropriate questions are never asked. As with the comparison between bipolar disorder and borderline personality disorder, the nature of affective symptoms potentially differs in borderline personality disorder in young people, and this is likely to have important implications for treatment and prognosis.

Conclusion

Borderline personality disorder has been shown to be a reliable and valid disorder in adolescents and young adults. Borderline- and mood-related psychopathology become clinically prominent across the same developmental period, from puberty through to young adulthood, and they frequently co-occur. Borderline personality and mood disorders share many common risk factors and precursors, rendering this aspect of clinical history taking of limited specificity. While the longitudinal outcomes for individuals presenting with such psychopathology are highly variable, evidence suggests that borderline- and mood-related psychopathology can intensify and/or mutually reinforce one another across this developmental period, possibly

crossing the threshold for a syndromal diagnosis. Regardless of whether an individual crosses such an arbitrary threshold, a substantial proportion of individuals will develop significant and persistent functional, vocational, and interpersonal impairment and disability.

Clearly, there is a need for intervention early in the course of these disorders, but the challenge is to balance the sensitivity and specificity of any early detection program. Effective early intervention improves the developmental and functional outcomes for these individuals. This must be balanced with the risk of diagnostic foreclosure, which can lead to the misapplication of diagnostic labels, stigma, inappropriate treatment, and other adverse outcomes.

Clinical Staging: A Heuristic and Pragmatic Framework to Guide Intervention

How might the above knowledge be integrated and applied in clinical practice? In adult psychiatric practice, the debate is often framed around the under-recognition of bipolar disorder or borderline personality disorder in people presenting for treatment of depression [95]. The reification of each separate syndrome leads to implications that one clinician or another is missing an "obvious case" and has foolishly applied the "wrong" treatment or is denying much needed specific treatment [7, 96].

A key problem in youth is the excessive focus upon each of these areas of risk research as separate domains in retrospective studies. In both bipolar disorder and borderline personality disorder, patients might present as depressed, experience mood changes, have early age of onset, have a history of abuse, engage in substance abuse, have impulsive behaviors, engage in self-harm, and have other comorbid disorders [97].

Critically, in youth mental health, patients most frequently present with admixtures of symptoms and a dynamic, evolving and uncertain clinical picture. A key problem, shared with adult psychiatry, appears to be that patients who present with depression are not further questioned as to the presence of symptoms of mania or hypomania [86] or borderline personality disorder [13].

Another key issue is disproportionate thinking with regard to intervention, with undue emphasis placed upon applying the most intensive interventions for adult phenotypes of the disorders (often pharmacotherapeutic) as first-line interventions [69] and a lack of emphasis upon psychosocial interventions. This is exemplified in the discussion about initiation of mood-stabilizing medications. On the one hand, there is a risk of medicating what might be a developmentally common and usually transitory nonclinical bipolar phenotype [67]. On the other hand, delay in initiation of mood stabilizers might diminish potential neuroprotective effects [53]. Furthermore, whatever the reasons for initiation of second-generation antipsychotic medications, there is evidence that longer-term harms might outweigh any benefits in young

people [98], especially when taking into account the lack of evidence for the effectiveness of these agents in bipolar II disorder or borderline personality disorder.

An alternative to the diagnostic category approach to prevention and early intervention is to develop a range of risk syndromes or warning signs for the development of a range of disorders [6, 99]. Key to this cross-diagnostic, "clinical staging" [100] approach is eschewing diagnostic categories and arbitrary age restrictions in favor of a focus on the severity and persistence of symptoms, the need for care, and the proportionality of any intervention.

Clinical staging involves mapping the development, progression, and extension of mental disorders over time and is essentially a more refined form of diagnosis. It is analogous to disease staging in general medicine. Its value is recognized in the treatment of malignancies and other potentially severe medical illnesses, where limiting the extension and secondary impacts of the disease, and improving quality of life and survival, all rely on the earliest possible delivery of effective interventions.

Clinical staging offers an integrating framework that is potentially more useful in determining which and what type of treatment will be most effective during a particular stage of disorder. Treatment needs will differ by phase or stage of disorder, with the possibility that interventions might be more benign and/or effective in earlier stages of disorder. Clinical staging is also much more consistent with evidence from developmental psychopathology that there are many paths to the development of disorders (equifinality) and diverse outcomes (multifinality) for those presenting with psychopathology [101].

Clinical staging differs from conventional diagnostic practice in that it defines not only the extent of progression of a disorder at a particular point in time but also where a person lies currently along the continuum of the course of an illness. The differentiation of early and milder clinical phenomena from those that accompany illness extension, progression, and chronicity lies at the heart of the concept, which makes it especially useful.

Table 9.1 illustrates the application of clinical staging, with a potential model for assessment of and intervention for mood disorders and borderline personality disorder (adapted from [53, 102]). This model recognizes the commonality of many of the risk factors for these disorders, their shared precursor symptoms and syndromes, and the diverse developmental pathways that any individual might take, especially those with an early stage disorder. Crucially, this framework outlines a proportionate clinical response to each stage of disorder. Suggested interventions are simpler and more benign during early stages of disorder (stages 0 and 1) and increase in intensity (and potential adverse effects) with disorder progression. In later stages of a disorder (stages 3 and 4), the risk of adverse effects becomes more justified when compared with the risk of not treating the disorder.

Many of the interventions suggested for early stages of disorder already exist, but their outcomes have not been assessed when used in this proposed model. Interventions for stages 1b and 2 are early in their development. Psychosocial interventions in youth include the Helping Young People Early (HYPE) program for borderline personality disorder [103], along with psychosocial interventions for bipolar disorder [104] and unipolar depression [105]. Low toxicity, novel

Table 9.1 A potential clinical staging model for bipolar disorder and borderline personality disorder

Clinical stage	Definition	Potential interventions
0	Increased risk of severe mood disorder or borderline personality disorder (e.g., family history, exposure to abuse or neglect, substance use)	Mental health literacy
	No specific current symptoms	Self-help
1a	Mild or nonspecific symptoms of mood disorder or borderline personality disorder (e.g., disturbances in attention, emotional regulation, and behavior)	Formal mental health literacy
		Family psychoeducation, parenting skills
		Substance abuse reduction
		Supportive counseling/problem solving
1b	Sub-threshold features of mood disorder or borderline personality disorder	1a plus phase-specific psychosocial intervention (e.g., cognitive behavioral therapy, HYPE early intervention for borderline personality disorder [103])
2	First episode of threshold mood disorder or borderline personality disorder	1b and case management, educational/vocational intervention/rehabilitation, family psychoeducation and support, specific time-limited psychotherapy, specific and targeted pharmacotherapy (e.g., mood stabilizer)
3a	Recurrence of sub-threshold mood or borderline personality disorder symptoms	2 and emphasis on maintenance medication and psychosocial strategies for full remission
3b	First threshold relapse of mood disorder or borderline personality disorder	3a and relapse prevention strategies
3c	Multiple relapses of mood disorder or borderline personality disorder	3b and combination mood stabilizers, intensive psychosocial interventions (e.g., dialectical behavior therapy)
4	Persistent unremitting disorder	3c and clozapine and other tertiary therapies, social participation despite disability

Adapted from [53, 102]

pharmacotherapies might also be appropriate for stages 1b and 2. Examples include *N-acetylcysteine* for bipolar disorder [106] or omega-3 fatty acids, which have evidence to support their use in both mood and borderline personality disorders from stage 2 onwards [107–109].

This clinical staging model for mood and borderline personality disorders will necessarily evolve and become more sophisticated with evolving knowledge about developmental pathways for these disorders (including indicative biological and endophenotypic markers) and novel interventions. It provides a starting point for both diagnosis and treatment development.

References

1. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62(6):593–602.
2. de Girolamo G, Dagani J, Purcell R, Cocchi A, McGorry PD. Age of onset of mental disorders and use of mental health services: needs, opportunities and obstacles. Epidemiol Psychiatr Serv. 2012;21:47–57.
3. Chanen AM, McCutcheon LK. Prevention and early intervention for borderline personality disorder: current status and recent evidence. Br J Psychiatry. 2013;202(S54):s24–9.
4. Cohen P, Crawford TN, Johnson JG, Kasen S. The children in the community study of developmental course of personality disorder. J Pers Disord. 2005;19(5):466–86.
5. Paris J. Personality disorders begin in adolescence. J Can Acad Child Adolesc Psychiatry. 2013;22(3):195–6.
6. McGorry PD. Early clinical phenotypes and risk for serious mental disorders in young people: need for care precedes traditional diagnoses in mood and psychotic disorders. Can J Psychiatry. 2013;58(1):19–21.
7. Paris J. Personality disorders and mood disorders: phenomenological resemblances vs. pathogenetic pathways. J Pers Disord. 2010;24(1):3–13.
8. Perugi G, Angst J, Azorin JM, Bowden C, Vieta E, Young AH. The bipolar-borderline personality disorders connection in major depressive patients. Acta Psychiatr Scand. 2013; 128:376–83.
9. Galione J, Zimmerman M. A comparison of depressed patients with and without borderline personality disorder: implications for interpreting studies of the validity of the bipolar spectrum. J Pers Disord. 2010;24(6):763–72.
10. Berkson J. Limitations of the application of fourfold table analysis to hospital data. Biom Bull. 1946;2:47–53.
11. Cicchetti D, Toth SL. The past achievements and future promises of developmental psychopathology: the coming of age of a discipline. J Child Psychol Psychiatry. 2009;50(1–2): 16–25.
12. APA. Diagnostic and statistical manual of mental disorders. 3rd ed. Washington, DC: American Psychiatric Association; 1980.
13. Chanen AM, McCutcheon LK. Personality disorder in adolescence: the diagnosis that dare not speak its name. Pers Ment Health. 2008;2(1):35–41.
14. National Collaborating Centre for Mental Health. Borderline personality disorder: treatment and management. London: National Institute for Health and Clinical Excellence; 2009. CG78 Contract No.: 78.
15. National Health and Medical Research Council. Clinical practice guideline for the management of borderline personality disorder. Melbourne: National Health and Medical Research Council; 2012.
16. Tackett JL, Balsis S, Oltmanns TF, Krueger RF. A unifying perspective on personality pathology across the life span: developmental considerations for the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders. Dev Psychopathol. 2009;21(3):687–713.
17. Chanen AM, Jovev M, McCutcheon L, Jackson HJ, McGorry PD. Borderline personality disorder in young people and the prospects for prevention and early intervention. Curr Psychiatry Rev. 2008;4(1):48–57.
18. Miller AL, Muehlenkamp JJ, Jacobson CM. Fact or fiction: diagnosing borderline personality disorder in adolescents. Clin Psychol Rev. 2008;28(6):969–81.
19. Chanen AM, Jovev M, Jackson HJ. Adaptive functioning and psychiatric symptoms in adolescents with borderline personality disorder. J Clin Psychiatry. 2007;68(2):297–306.
20. Chanen AM, Jovev M, Djaja D, McDougall E, Yuen HP, Rawlings D, et al. Screening for borderline personality disorder in outpatient youth. J Pers Disord. 2008;22(4):353–64.

21. Ullrich S, Coid J. The age distribution of self-reported personality disorder traits in a household population. J Pers Disord. 2009;23(2):187–200.
22. Johnson JG, Cohen P, Kasen S, Skodol AE, Hamagami F, Brook JS. Age-related change in personality disorder trait levels between early adolescence and adulthood: a community-based longitudinal investigation. Acta Psychiatr Scand. 2000;102(4):265–75.
23. Samuels J, Eaton WW, Bienvenu O, Brown C, Costa PT, Nestadt G. Prevalence and correlates of personality disorders in a community sample. Br J Psychiatry. 2002;180(6):536–42.
24. Bernstein DP, Cohen P, Velez CN, Schwab-Stone M, Siever LJ, Shinsato L. Prevalence and stability of the DSM-III-R personality disorders in a community-based survey of adolescents. Am J Psychiatry. 1993;150(8):1237–43.
25. Moran P, Coffey C, Mann A, Carlin JB, Patton GC. Personality and substance use disorders in young adults. Br J Psychiatry. 2006;188(4):374–9.
26. Chanen AM, Jackson HJ, McGorry PD, Allott KA, Clarkson V, Yuen HP. Two-year stability of personality disorder in older adolescent outpatients. J Pers Disord. 2004;18(6):526–41.
27. Kaess M, von Ceumern-Lindenstjerna I-A, Parzer P, Chanen AM, Mundt C, Resch F, et al. Axis I and II comorbidity and psychosocial functioning in female adolescents with borderline personality disorder. Psychopathology. 2012;46(1):52–62.
28. Crawford TN, Cohen P, First MB, Skodol AE, Johnson JG, Kasen S. Comorbid Axis I and Axis II disorders in early adolescence: prognosis 20 years later. Arch Gen Psychiatry. 2008;65(6):641–8.
29. Winograd G, Cohen P, Chen H. Adolescent borderline symptoms in the community: prognosis for functioning over 20 years. J Child Psychol Psychiatry. 2008;49(9):933–41.
30. Stepp SD, Pilkonis PA, Hipwell AE, Loeber R, Stouthamer-Loeber M. Stability of borderline personality disorder features in girls. J Pers Disord. 2010;24(4):460–72.
31. Crick NR, Murray-Close D, Woods K. Borderline personality features in childhood: a short-term longitudinal study. Dev Psychopathol. 2005;17(4):1051–70.
32. Cohen P. Childhood risks for young adult symptoms of personality disorder: method and substance. Multivariate Behav Res. 1996;31(1):121–48.
33. Bernstein DP, Cohen P, Skodol A, Bezirganian S, Brook J. Childhood antecedents of adolescent personality disorders. Am J Psychiatry. 1996;153(7):907–13.
34. Kasen S, Cohen P, Skodol AE, Johnson JG, Brook JS. Influence of child and adolescent psychiatric disorders on young adult personality disorder. Am J Psychiatry. 1999;156(10):1529–35.
35. Crawford TN, Cohen P, Johnson JG, Kasen S, First MB, Gordon K, et al. Self-reported personality disorder in the Children in the Community Sample: convergent and prospective validity in late adolescence and adulthood. J Pers Disord. 2005;19(1):30–52.
36. Chanen AM, Kaess M. Developmental pathways toward borderline personality disorder. Curr Psychiatry Rep. 2012;14(1):45–53.
37. Kraemer HC, Kazdin AE, Offord DR, Kessler RC, Jensen PS, Kupfer DJ. Coming to terms with the terms of risk. Arch Gen Psychiatry. 1997;54(4):337–43.
38. Eaton WW, Badawi M, Melton B. Prodromes and precursors: epidemiologic data for primary prevention of disorders with slow onset. Am J Psychiatry. 1995;152(7):967–72.
39. Crawford TN, Cohen PR, Chen H, Anglin DM, Ehrensaft M. Early maternal separation and the trajectory of borderline personality disorder symptoms. Dev Psychopathol. 2009;21(3):1013–30.
40. Carlson EA, Egeland B, Sroufe LA. A prospective investigation of the development of borderline personality symptoms. Dev Psychopathol. 2009;21(4):1311–34.
41. Rohde P, Lewinsohn PM, Kahler CW, Seeley JR, Brown RA. Natural course of alcohol use disorders from adolescence to young adulthood. J Am Acad Child Adolesc Psychiatry. 2001;40(1):83–90.
42. Thatcher DL, Cornelius JR, Clark DB. Adolescent alcohol use disorders predict adult borderline personality. Addict Behav. 2005;30(9):1709–24.
43. Stepp SD, Burke JD, Hipwell AE, Loeber R. Trajectories of attention deficit hyperactivity disorder and oppositional defiant disorder symptoms as precursors of borderline personality disorder symptoms in adolescent girls. J Abnorm Child Psychol. 2012;40:7–20.

44. Burke JD, Stepp SD. Adolescent disruptive behavior and borderline personality disorder symptoms in young adult men. J Abnorm Child Psychol. 2012;40(1):35–44.
45. Leichsenring F, Leibing E, Kruse J, New AS, Leweke F. Borderline personality disorder. Lancet. 2011;377(9759):74–84.
46. Zanarini MC, Frankenburg FR, Ridolfi ME, Jager-Hyman S, Hennen J, Gunderson JG. Reported childhood onset of self-mutilation among borderline patients. J Pers Disord. 2006;20(1):9–15.
47. Nock MK. Self-injury. Annu Rev Clin Psychol. 2010;6:339–63.
48. Brunner R, Parzer P, Haffner J, Steen R, Roos J, Klett M, et al. Prevalence and psychological correlates of occasional and repetitive deliberate self-harm in adolescents. Arch Pediatr Adolesc Med. 2007;161(7):641–9.
49. Nock MK, Joiner JTE, Gordon KH, Lloyd-Richardson E, Prinstein MJ. Non-suicidal self-injury among adolescents: diagnostic correlates and relation to suicide attempts. Psychiatry Res. 2006;144(1):65–72.
50. Muehlenkamp JJ, Ertelt TW, Miller AL, Claes L. Borderline personality symptoms differentiate non-suicidal and suicidal self-injury in ethnically diverse adolescent outpatients. J Child Psychol Psychiatry. 2011;52(2):148–55.
51. Jacobson CM, Muehlenkamp JJ, Miller AL, Turner JB. Psychiatric impairment among adolescents engaging in different types of deliberate self-harm. J Clin Child Adolesc Psychol. 2008;37(2):363–75.
52. Cohen P, Chen H, Kasen S, Johnson JG, Crawford T, Gordon K. Adolescent Cluster A personality disorder symptoms, role assumption in the transition to adulthood, and resolution or persistence of symptoms. Dev Psychopathol. 2005;17(2):549–68.
53. Berk M, Berk L, Dodd S, Cotton S, Macneil C, Daglas R, et al. Stage managing bipolar disorder. Bipolar Disord. 2013. DOI:10.1111/bdi.12099.
54. Lish JD, Dime-Meenan S, Whybrow PC, Price RA, Hirschfeld RM. The National Depressive and Manic-depressive Association (DMDA) survey of bipolar members. J Affect Disord. 1994;31(4):281–94.
55. Berk M, Hallam KT, McGorry PD. The potential utility of a staging model as a course specifier: a bipolar disorder perspective. J Affect Disord. 2007;100(1–3):279–81.
56. Bechdolf A, Ratheesh A, Wood SJ, Tecic T, Conus P, Nelson B, et al. Rationale and first results of developing at-risk (prodromal) criteria for bipolar disorder. Curr Pharm Des. 2012;18(4):358–75.
57. Lapalme M, Hodgins S, LaRoche C. Children of parents with bipolar disorder: a metaanalysis of risk for mental disorders. Can J Psychiatry. 1997;42(6):623–31.
58. Oquendo MA, Ellis SP, Chesin MS, Birmaher B, Zelazny J, Tin A, et al. Familial transmission of parental mood disorders: unipolar and bipolar disorders in offspring. Bipolar Disord. 2013;15:764–73.
59. Ryden E, Thase ME, Straht D, Aberg-Wistedt A, Bejerot S, Landen M. A history of childhood attention-deficit hyperactivity disorder (ADHD) impacts clinical outcome in adult bipolar patients regardless of current ADHD. Acta Psychiatr Scand. 2009;120(3):239–46.
60. Faraone SV, Biederman J, Mennin D, Wozniak J, Spencer T. Attention-deficit hyperactivity disorder with bipolar disorder: a familial subtype? J Am Acad Child Adolesc Psychiatry. 1997;36(10):1378–87; discussion 87–90.
61. Marchand WR, Wirth L, Simon C. Adverse life events and pediatric bipolar disorder in a community mental health setting. Community Ment Health J. 2005;41(1):67–75.
62. Garno JL, Goldberg JF, Ramirez PM, Ritzler BA. Impact of childhood abuse on the clinical course of bipolar disorder. Br J Psychiatry. 2005;186:121–5.
63. Strakowski SM, DelBello MP. The co-occurrence of bipolar and substance use disorders. Clin Psychol Rev. 2000;20(2):191–206.
64. Young LT, Bagby RM, Cooke RG, Parker JD, Levitt AJ, Joffe RT. A comparison of Tridimensional Personality Questionnaire dimensions in bipolar disorder and unipolar depression. Psychiatry Res. 1995;58(2):139–43.

65. Thompson KN, Conus PO, Ward JL, Phillips LJ, Koutsogiannis J, Leicester S, et al. The initial prodrome to bipolar affective disorder: prospective case studies. J Affect Disord. 2003;77(1):79–85.
66. Conus P, Ward J, Hallam KT, Lucas N, Macneil C, McGorry PD, et al. The proximal prodrome to first episode mania. Bipolar Disord. 2008;10(5):555–65.
67. Tijssen MJ, van Os J, Wittchen HU, Lieb R, Beesdo K, Mengelers R, et al. Prediction of transition from common adolescent bipolar experiences to bipolar disorder: 10-year study. Br J Psychiatry. 2010;196(2):102–8.
68. Birmaher B, Axelson D, Goldstein B, Strober M, Gill MK, Hunt J, et al. Four-year longitudinal course of children and adolescents with bipolar spectrum disorders: the Course and Outcome of Bipolar Youth (COBY) study. Am J Psychiatry. 2009;166(7):795–804.
69. Leibenluft E. Severe mood dysregulation, irritability, and the diagnostic boundaries of bipolar disorder in youths. Am J Psychiatry. 2011;168(2):129–42.
70. Bell RQ. Multiple-risk cohorts and segmenting risk as solutions to the problem of false positives in risk for the major psychoses. Psychiatry. 1992;55(4):370–81.
71. Allen NB, Hetrick S, Simmons JG, Hickie IB. Early intervention for depressive disorders in young people: the opportunity and the (lack of) evidence. Med J Aust. 2007;187(7):S15–7.
72. Kessler RC, Chiu WT, Demler O, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the national comorbidity survey replication. Arch Gen Psychiatry. 2005;62(6):617–27.
73. Costello EJ, Pine DS, Hammen C, March JS, Plotsky PM, Weissman MM, et al. Development and natural history of mood disorders. Biol Psychiatry. 2002;52(6):529–42.
74. Gladstone TR, Beardslee WR, O'Connor EE. The prevention of adolescent depression. Psychiatr Clin North Am. 2011;34(1):35–52.
75. Hill J, Pickles A, Rollinson L, Davies R, Byatt M. Juvenile- versus adult-onset depression: multiple differences imply different pathways. Psychol Med. 2004;34(8):1483–93.
76. Fernando K, Carter JD, Frampton CM, Luty SE, McKenzie J, Mulder RT, et al. Childhood-, teenage-, and adult-onset depression: diagnostic and individual characteristics in a clinical sample. Compr Psychiatry. 2011;52(6):623–9.
77. Vandeleur C, Rothen S, Gholam-Rezaee M, Castelao E, Vidal S, Favre S, et al. Mental disorders in offspring of parents with bipolar and major depressive disorders. Bipolar Disord. 2012;14(6):641–53.
78. Hankin BL. Future directions in vulnerability to depression among youth: integrating risk factors and processes across multiple levels of analysis. J Clin Child Adolesc Psychol. 2012;41(5):695–718.
79. Johnson JG, Cohen P, Kasen S, Brook JS. Personality disorder traits associated with risk for unipolar depression during middle adulthood. Psychiatry Res. 2005;136(2–3):113–21.
80. Dolan-Sewell RT, Krueger RF, Shea M. Co-occurrence with syndrome disorders. In: Livesley WJ, editor. Handbook of personality disorders: theory, research, and treatment. New York: Guilford Press; 2001. p. 84–104.
81. Barrachina J, Pascual JC, Ferrer M, Soler J, Rufat MJ, Andion O, et al. Axis II comorbidity in borderline personality disorder is influenced by sex, age, and clinical severity. Compr Psychiatry. 2011;52(6):725–30.
82. Eaton NR, Krueger RF, Keyes KM, Skodol AE, Markon KE, Grant BF, et al. Borderline personality disorder co-morbidity: relationship to the internalizing-externalizing structure of common mental disorders. Psychol Med. 2011;41(5):1041–50.
83. Lenzenweger MF, Lane MC, Loranger AW, Kessler RC. DSM-IV personality disorders in the National Comorbidity Survey Replication. Biol Psychiatry. 2007;62(6):553–64.
84. Krueger RF, Markon KE. Reinterpreting comorbidity: a model-based approach to understanding and classifying psychopathology. Annu Rev Clin Psychol. 2006;2:111–33.
85. Paris J, Gunderson J, Weinberg I. The interface between borderline personality disorder and bipolar spectrum disorders. Compr Psychiatry. 2007;48(2):145–54.
86. Benazzi F. A relationship between bipolar II disorder and borderline personality disorder? Prog Neuropsychopharmacol Biol Psychiatry. 2008;32(4):1022–9.

87. Barroilhet S, Vöhringer PA, Ghaemi SN. Borderline versus bipolar: differences matter. Acta Psychiatr Scand. 2013;128(5):385–6.
88. Renaud S, Corbalan F, Beaulieu S. Differential diagnosis of bipolar affective disorder type II and borderline personality disorder: analysis of the affective dimension. Compr Psychiatry. 2012;53(7):952–61.
89. Bassett D. Borderline personality disorder and bipolar affective disorder. Spectra or spectre? A review. Aust N Z J Psychiatry. 2012;46(4):327–39.
90. Smith DJ, Muir WJ, Blackwood DHR. Borderline personality disorder characteristics in young adults with recurrent mood disorders: a comparison of bipolar and unipolar depression. J Affect Disord. 2005;87(1):17–23.
91. Moor S, Crowe M, Luty SE, Carter JD, Joyce PR. Effects of comorbidity and early age of onset in young people with bipolar disorder on self harming behaviour and suicide attempts. J Affect Disord. 2012;136:1212–5.
92. Baethge C, Baldessarini RJ, Khalsa HM, Hennen J, Salvatore P, Tohen M. Substance abuse in first-episode bipolar I disorder: indications for early intervention. Am J Psychiatry. 2005; 162(5):1008–10.
93. Berk M, Dodd S, Callaly P, Berk L, Fitzgerald P, de Castella AR, et al. History of illness prior to a diagnosis of bipolar disorder or schizoaffective disorder. J Affect Disord. 2007;103(1–3): 181–6.
94. Luca M, Luca A, Calandra C. Borderline personality disorder and depression: an update. Psychiatry Q. 2012;83(3):281–92.
95. Zimmerman ME, Morgan TA. The relationship between borderline personality disorder and bipolar disorder. Dialogues Clin Neurosci. 2013;15(2):155–69.
96. Matza LS, Rajagopalan KS, Thompson CL, de Lissovoy G. Misdiagnosed patients with bipolar disorder: comorbidities, treatment patterns, and direct treatment costs. J Clin Psychiatry. 2005;66(11):1432–40.
97. Zimmerman ME, Galione JN, Ruggero CJ, Chelminski I, Young D, Dalrymple K, et al. Screening for bipolar disorder and finding borderline personality disorder. J Clin Psychiatry. 2010;71(9):1212–7.
98. Correll CU, Manu P, Olshanskiy V, Napolitano B, Kane JM, Malhotra AK. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. JAMA. 2009;302(16):1765–73.
99. McGorry PD, van Os J. Redeeming diagnosis in psychiatry: timing versus specificity. Lancet. 2013;381(9863):343–5.
100. McGorry PD. Risk syndromes, clinical staging and DSM V: new diagnostic infrastructure for early intervention in psychiatry. Schizophr Res. 2010;120(1–3):49–53.
101. Cicchetti D, Rogosch FA. A developmental psychopathology perspective on adolescence. J Consult Clin Psychol. 2002;70(1):6–20.
102. McGorry PD, Hickie IB, Yung AR, Pantelis C, Jackson HJ. Clinical staging of psychiatric disorders: a heuristic framework for choosing earlier, safer and more effective interventions. Aust N Z J Psychiatry. 2006;40(8):616–22.
103. Chanen AM, McCutcheon L, Germano D, Nistico H, Jackson HJ, McGorry PD. The HYPE Clinic: an early intervention service for borderline personality disorder. J Psychiatr Pract. 2009;15(3):163–72.
104. Macneil CA, Hallam K, Conus P, Henry L, Kader L, Berk M. Are we missing opportunities for early intervention in bipolar disorder? Expert Rev Neurother. 2012;12(1):5–7.
105. Garber J, Clarke GN, Weersing VR, Beardslee WR, Brent DA, Gladstone TR, et al. Prevention of depression in at-risk adolescents: a randomized controlled trial. JAMA. 2009;301(21): 2215–24.
106. Berk M, Copolov DL, Dean O, Lu K, Jeavons S, Schapkaitz I, et al. N-acetyl cysteine for depressive symptoms in bipolar disorder—a double-blind randomized placebo-controlled trial. Biol Psychiatry. 2008;64(6):468–75.
107. Amminger GP, Chanen AM, Ohmann S, Klier C, Mossaheb N, Bechdolf A, et al. Ω-3 fatty acid supplementation in adolescents with borderline personality disorder and ultra-high risk

criteria for psychosis: a post-hoc subgroup analysis of a double-blind randomised controlled trial. Can J Psychiatry. 2013;58(7):402–8.
108. Zanarini MC, Frankenburg FR. Omega-3 fatty acid treatment of women with borderline personality disorder: a double-blind, placebo-controlled pilot study. Am J Psychiatry. 2003; 160(1):167–9.
109. Sarris J, Mischoulon D, Schweitzer I. Omega-3 for bipolar disorder: meta-analyses of use in mania and bipolar depression. J Clin Psychiatry. 2012;73(1):81–6.

Chapter 10
Borderline Personality Disorder and Mood Disorders: Longitudinal Course and Interactions

Andrew E. Skodol

Introduction

Borderline personality disorder (BPD) is often misdiagnosed as a mood disorder, especially bipolar disorder [1, 2]. Many variants of bipolar disorder have been conceived, such as bipolar II [3], bipolar III [4], and bipolar IV [5] in order to account for atypical features, a more chronic course, and lack of or adverse responses to standard psychopharmacologic treatments of bipolar disorder. Similarly, major depressive disorder (MDD) may have a more chronic than episodic course with waxing and waning of symptoms or incomplete remission with subthreshold symptoms [6]. Mood disorder diagnostic variants that broaden the definitions of disorders often lead in clinical practice to the inappropriate use of medications in false-positive cases [7], to a proliferation of medication changes, and sometimes to extensive and harmful polypharmacy aimed at addressing clinical problems that may well be the result of BPD, occurring either alone or as a comorbid condition. Since BPD and mood disorders frequently co-occur [8], examining the longitudinal course of BPD and comorbid mood disorders and their interactions over time may shed light not only on the disorder of primary importance but also, as a result, on the need to recognize and treat BPD with psychotherapy [9–11] in order to achieve optimal outcomes in such cases.

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Naturalistic Studies of Clinical Course in Personality Disorder

Selected results of four large-scale studies of the naturalistic course of personality disorders and mood disorders will be reviewed in this chapter. The studies are the Collaborative Longitudinal Personality Disorders Study (CLPS) [12, 13], the McLean Study of Adult Development (MSAD) [14], the National Epidemiologic Study of Alcohol and Related Conditions (NESARC) [15, 16], and the Children in the Community Study (CICS) [17]. These studies were conducted on patient (CLPS and MSAD) and community (NESARC and CICS) populations, leading to a greater degree of confidence in findings that converge.

Collaborative Longitudinal Personality Disorders Study (CLPS)

The CLPS [12, 13] is a multisite, NIMH-funded longitudinal study of the natural course of personality disorders. Participating sites are at Brown, Columbia (now in collaboration with the University of Arizona), Harvard, Yale, and Texas A&M Universities. The aims of the CLPS have been to determine the stability of personality disorder diagnoses and criteria, personality traits, and functional impairment and to determine predictors of clinical course. The original CLPS sample recruited 668 treatment-seeking or recently treated patients who were diagnosed with one of four DSM-IV personality disorders—schizotypal (STPD), borderline (BPD), avoidant (AVPD), or obsessive-compulsive (OCPD)—or with major depressive disorder (MDD) and no personality disorder. Personality disorders were diagnosed at baseline with the semi-structured Diagnostic Interview for Personality Disorders-IV (DIPD-IV) [18] and confirmed by at least one other personality assessment method. Mood and other nonpersonality disorders were diagnosed with the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) [19]. This original sample was supplemented with the recruitment of 65 additional minority patients to ensure adequate power to test differences between Caucasian, African-American, and Hispanic patients with the four personality disorders on various outcomes. The original CLPS sample completed 10 years of annual follow-up.

To provide more detailed data on persistence vs. change in personality disorder criteria and diagnoses, the interview used to make intake personality disorder diagnoses, the DIPD-IV, was modified in the CLPS to provide monthly ratings of the presence or absence of individual criteria for each of the four disorders under study. This approach was based on the method used to track the course of Axis I disorders in the study, the Longitudinal Interval Follow-up Evaluation (LIFE) [20], resulting in similar ratings of the course of both personality disorders and Axis I disorders in terms of the timing of assessments and the levels of symptoms or criteria present. The monthly ratings of personality disorder criteria also allow determination of various definitions of improvement or remission, based on the number of criteria present and the length of time present or absent. The LIFE has been the central

measure of course used in the most comprehensive longitudinal study to date of mood disorders, the Collaborative Depression Study (CDS) [21]. The similarity of methods allows for a comparison of the stability and course of the four CLPS personality disorders with that of several mood disorders and for documenting interactions in the course of personality disorders and mood disorders over time. Primary questions for the CLPS have been whether personality disorders are more diagnostically stable than mood disorders and, when changes occur, which disorder appears to exert an effect on the other, as evidenced by the relative timing of changes in the expression of each type of disorder.

The McLean Study of Adult Development (MSAD)

The MSAD [14] was the first NIMH-funded prospective study of the course and outcome of borderline personality disorder. The MSAD sample consists of 290 patients with BPD, diagnosed by both the DIPD-IV [18] and the Revised Diagnostic Interview for Borderlines [22], who were inpatients at McLean Hospital in the early 1990s, and 72 other hospitalized patients who were diagnosed with other personality disorders (OPDs). This comparison group included approximately 4 % with cluster A personality disorders, 18 % with other non-borderline cluster B personality disorders, 33 % with cluster C personality disorders, and 53 % with personality disorder not otherwise specified (PDNOS). The sample has been followed every 2 years for more than 16 years. Remission has been defined as no longer meeting criteria for the index personality disorder for a period of at least 2 years.

The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)

Participants of interest were respondents in Waves 1 and 2 of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) [15, 16]. The target population was the civilian non-institutionalized population 18 years and older residing in households and group quarters (e.g., college quarters, group homes, boarding houses, and non-transient hotels) in the United States. Blacks, Hispanics, and adults ages 18–24 were over-sampled, with data adjusted for over-sampling, household- and person-level nonresponse. Of the 43,093 respondents interviewed at Wave 1, census-defined eligible respondents for Wave 2 reinterviews included those not deceased ($N = 1{,}403$); deported and mentally or physically impaired ($N = 781$); or on active military duty ($N = 950$). In Wave 2, 34,653 of 39,959 eligible respondents were reinterviewed, for a response rate of 86.7 %. Sample weights further adjusted for Wave 2 nonresponse [16]. Overall, most respondents were female, white, over the age of 40, married or cohabiting, and had at least a college education.

In-person interviews were conducted at both waves by experienced lay interviewers with extensive training and supervision. Interviewers administered the NIAAA Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-IV Version (AUDADIS-IV) [23], a fully structured diagnostic interview developed to assess substance use and other mental disorders in large-scale surveys. Computer algorithms produced diagnoses of DSM-IV Axis I disorders and all DSM-IV PDs. Major depressive disorder (MDD) was defined according to DSM-IV inclusion criteria, including all symptom, duration, and clinical significance (i.e., distress or impairment) criteria. Diagnoses additionally required that the disorders be "primary," i.e., not substance induced or due to a general medical condition.

At Wave 1, criteria for MDD were assessed in two time frames: (1) current, i.e., during the last 12 months, and (2) prior to the last 12 months. At Wave 2, 3 years later, these criteria were again assessed in two time frames covering the time period between Waves 1 and 2. *Persistent* MDD was defined as meeting full criteria for current MDD at Wave 1 and full criteria for MDD throughout the entire 3-year follow-up. *Recurrent* MDD was defined as meeting full criteria at Wave 1 and again during the last 12 months at Wave 2, but not during the first 24 months after the Wave 1 interview. The impact of all DSM-IV personality disorders on the 3-year persistence and recurrence of MDD was examined.

The Children in the Community Study (CICS)

The CICS [17] is a longitudinal study of a representative sample of approximately 800 children, who were originally recruited (with their mothers) in upstate New York in 1975, when they were between 1 and 10 years of age. They have been followed now periodically for 30 years. Originally, the study was designed to assess level of need for children's services in the community. When first followed-up in 1983, the focus of the study shifted to predictors of Axis I disorders in early adolescence, but an interest in the development of personality disorders in this age group also existed. Using various methods, personality disorders have been assessed four times: in 1983, when the children were at mean age 14; between 1985 and 1986, when they were at mean age 16; between 1991 and 1993, at mean age 22; and between 2001 and 2004, at mean age 33. The relationships of Axis I disorders and personality disorders have been studied over the follow-up periods.

Course of BPD and Depressive Disorders

Borderline personality disorder (BPD) was one of three personality disorders (the others being avoidant and dependent) that were found most often to co-occur with mood disorders, especially depressive disorders, in the CLPS [8]. The severity of depression, recurrence of depressive episodes, and comorbid dysthymic disorder

predicted co-occurrence of major depressive disorder (MDD) with BPD. These results are consistent with the view that a history of a depressive disorder with an insidious onset, recurrence, chronicity, and progression in severity is suggestive of the presence of BPD in young adults.

The 24-month natural course of remission from MDD as a function of personality disorder comorbidity was examined prospectively in the CLPS [24]. The overall remission rate for MDD was 73.5 %. Patients with MDD who had BPD (or STPD or AVPD) as their primary PD diagnosis had a significantly longer time to remission from MDD than did patients with MDD without a co-occurring personality disorder. These personality disorders were robust predictors of slowed remission from MDD even when controlling for other factors often believed to exert a negative prognostic effect on MDD, such as co-occurring dysthymia, other Axis I disorder comorbidity, early age at onset of MDD, and a pattern of MDD recurrence. The relationship of comorbid personality disorder to MDD remission was examined again after 6 years of follow-up [25]. Patients with personality disorders continued to have a significantly longer time to remission of MDD. Of the patients whose MDD remitted, 70 % relapsed. Patients with MDD and comorbid BPD (or OCPD) had significantly shorter times to relapse than patients with MDD and no personality disorder. Research criteria for depressive personality disorder also resulted in a lower likelihood of remission of baseline MDD at 2-year follow-up, while comorbid dysthymic disorder did not [26]. At 6 years, already recurrent MDD predicted shorter time to future relapse, but again dysthymic disorder did not.

In another examination of predictors of recurrences and new onsets of MDD over 6 years of follow-up [27], patients with BPD were more likely to have recurrences of MDD and about equally likely to have new onsets compared to patients with other personality disorders (OPDs). The total number of BPD criteria and the number of BPD affective criteria were predictive of new onsets. The total number of BPD criteria and the number of BPD affective, impulsive, and relational criteria each predicted recurrences. There was no evidence that the number or the subgroups of BPD criteria were more predictive in patients diagnosed with BPD than in patients diagnosed with OPDs, suggesting that these dimensions of borderline personality psychopathology have prognostic significance for MDD outcomes independent of the DSM-IV (now DSM-5 Section II, as well) personality disorder categorical diagnosis.

At the 10-year CLPS follow-up [28], BPD again had a clearly significant negative effect on time to remission of MDD (i.e., longer time to remission) and a mildly significant negative effect on time to relapse (i.e., shorter time to relapse). MDD also had a significant negative effect on time to remission and time to relapse of BPD, so the relationships between the two disorders were reciprocal.

Patients with BPD in the MSAD experienced declining rates of many Axis I disorders over 6 years [29]. Rates of both mood and anxiety disorders continued to remain high, however. Consistent with the MSAD findings on the beneficial effects of remission on functioning, patients with BPD who had a remission experienced declines in all comorbid Axis I disorders assessed, while those who did not remit reported stable rates. Substance use disorders, but not mood or other Axis I disorders, had a negative effect on remission from BPD.

Although prospective studies of patient samples such as CLPS and the MSAD provide important information, patient studies may be biased by numerous confounds and selection factors [30]. To better understand the course of MDD and its predictors, prospective epidemiological studies are needed. The effects of specific personality disorder comorbidity on the course of MDD in a nationally representative sample were evaluated in the National Epidemiologic Survey on Alcoholism and Related Conditions (NESARC) [31]. The 3-year follow-up interview of the large NESARC sample provided the opportunity to determine the rates of persistence and recurrence of MDD in the community and the specific effects of all DSM-IV personality disorders compared to each other on its course while also allowing for multivariate analyses to account for a number of other potential predictors of chronicity. These data presented a unique opportunity to confirm the hypothesis generated in the CLPS clinical populations [24, 25] that personality disorders exert a strong, independent negative impact on the course of MDD.

15.1 % of NESARC participants had persistent MDD and 7.3 % of those who remitted had a recurrence during the 3 years of follow-up [31]. Univariate analyses indicated that avoidant, borderline, histrionic, paranoid, schizoid, and schizotypal personality disorders all elevated the risk for persistence of MDD. With Axis I comorbidity controlled, all but histrionic personality disorder remained significant. With all other personality disorders controlled, borderline and schizotypal remained significant predictors. In final, multivariate analyses that controlled for age at onset of MDD, number of previous episodes, duration of current episode, family history, and treatment, BPD remained a robust predictor of MDD persistence. Neither personality disorders nor other clinical variables predicted recurrence. Thus, in this nationally representative sample of adults with MDD, BPD robustly predicted persistence, a finding that converges with clinical studies.

In the CICS, adolescent or young adult cluster A personality disorder symptoms increased risk of subsequent mood as well as eating, anxiety, and disruptive behavior disorders. Adolescent or young adult cluster B symptoms increased risk of subsequent mood, anxiety, eating, disruptive, *and* substance use disorders. Cluster C symptoms increased risk of subsequent mood, anxiety, and disruptive behavior, but not eating or substance use, disorders [32–35]. Significantly, childhood MDD in the CICS increased the risk of young adult personality disorders, specifically dependent, antisocial, passive-aggressive, and histrionic PDs, but not borderline PD [36, 37]. Childhood or adolescent depression (and other psychopathologies) may set in motion a chain of maladaptive behaviors and environmental responses that lead to personality psychopathology. Personality disorders, therefore, may represent alternative pathways of continuity for MDD across the transition from childhood to adulthood, reminiscent of the findings on depressive and personality disorder co-occurrence reported earlier from the CLPS [8]. The lack of convergence in the CICS on the specificity of the relationships of mood and particular personality disorders, especially BPD, found in other longitudinal studies raises some questions. Differences could be due to different methods for assessing psychopathology in the studies, or perhaps current categorical conceptualizations of depressive and personality disorders may not be the ideal units of analysis for studying their interrelationships.

Course of BPD and Bipolar Disorders

Considerably less is known from prospective longitudinal studies about the relationships between BPD and bipolar disorders than between BPD and depressive disorders. In an examination of recurrences and new onsets of bipolar disorder over 4 years of follow-up, however, significantly more patients with BPD developed new onsets of bipolar I and II disorders (7.9 %), compared to patients with OPD (3.1 %) [38]. Within the OPD sample, those with co-occurring bipolar disorder were more apt to develop new onsets of BPD than were those without co-occurring bipolar disorder. This study also showed that in the BPD sample, co-occurrence of bipolar I or bipolar II disorders did not much affect the course of BPD in terms of remission, functional level, or treatment utilization. At 10 years, BPD did not have a significant effect on the course of bipolar I or bipolar II, although the confidence intervals for the hazard ratios overlapped considerably due to the limited numbers of cases [39]. Neither bipolar I nor bipolar II had a statistically significant interaction with BPD with the exception of bipolar II, which had a negative effect on time to remission of BPD; however, again because of the low n's relative to MDD, the confidence intervals for the hazard ratios again overlapped.

Implications of Studies of Longitudinal Course

Research Implications

It is increasingly recognized that, despite conceptual distinctions, there is overlap in some of the psychopathology embedded in the criteria for mood disorders and personality disorders. One relevant model published over 20 years ago proposed that four psychobiological dimensions may underlie both the Axis I disorders and personality disorders: abnormalities in cognition and perception, affect regulation, impulsivity, and anxiety and inhibition [40]. This approach recognizes enduring vulnerabilities or propensities to manifest particular symptoms or behavior, very similar to the notion of personality traits, underlying Axis I disorders. From the perspective of personality, several models describe affective traits [41]. The Five-Factor Model (FFM) [42], for example, includes the trait domain of *neuroticism*, which is the enduring propensity to experience negative affects such as anxiety, depression, and irritability. Clark and colleagues have described a model of *positive* and *negative affectivity*, defining each as "…a stable, heritable, and highly general trait dimension with a multiplicity of aspects ranging from mood to behavior" [43]. They further describe these temperamental dimensions as vulnerabilities for the development of anxiety and depression [43]. The Alternative Model for personality disorders in DSM-5 Section III includes the trait domain of *negative affectivity* (NA), defined as "frequent and intense experiences of high levels of a wide range of negative emotions (e.g., anxiety, depression, guilt/shame, worry, anger, etc.), and

their behavioral (e.g., self-harm) and interpersonal (e.g., dependency) manifestations" [44]. The trait facet of *depressivity* within the domain of NA is defined as "feelings of being down, miserable, and/or hopeless; difficulty recovering from such moods; pessimism about the future; pervasive shame and/or guilt; feelings of inferior self worth; thoughts of suicide and suicidal behavior" and is one of the "B" (pathological personality trait) criteria for BPD in the DSM-5 Alternative Model. These trait dimensions have been shown to be stable over a period of 6–7 years in a nonclinical sample recruited as college students, at least with regard to rank order stability, although the mean level of negative affectivity showed a significant decrease [45]. As noted by Widiger [41], fluctuations in intensity of the affects associated with temperamental dimensions "…can at times reach clinically significant levels of maladaptivity and warrant a diagnosis of a mental disorder" [41].

Dimensions of temperament may help explain the chronicity of mood disorders, as these are enduring propensities to experience negative affects including depression. There may be increases in the intensity of such affects for periods of time, captured in the mood disorders as "episodes." In an examination of the timing of the improvements in the personality and Axis I disorders, significant reciprocal time-varying associations were found for BPD with MDD and for AVPD with social phobia [46]. The 10-year CLPS findings are notable for documenting strong reciprocal effects of BPD and co-occurring MDD upon each other's time to remission and time to relapse/onsets [28]. These findings extend those in earlier reports over briefer follow-up periods from CLPS [46–48] and are consistent with recent findings from the NESARC epidemiological sample [31] that also showed the strong effect of BPD status on the course of MDD. Finding a significant effect of change in MDD on BPD's course also supports the finding from the 2-year CLPS follow-up [46]. Furthermore, despite the relative instability of the personality disorder diagnoses in the CLPS sample, and significant decreases in the mean number of criteria present, the rank order of individuals on the number of criteria met for the disorders (i.e. the correlations over repeated assessments) was very high, indicating stability in terms of the kinds of criteria present [49]. Thus, it may be that both mood disorders and certain personality disorders, especially BPD, are characterized by enduring vulnerabilities, with periodic exacerbations that reach full diagnostic criteria for the various disorders at various times. Furthermore, personality disorders and mood disorders may share at least some of the same enduring vulnerabilities. A strong interaction of BPD and MDD, suggesting overlapping psychopathologies and etiologies, alongside weaker evidence for dependencies between BPD and bipolar disorder is consistent with data from family history studies that also show a possible, albeit uncertain, relationship between BPD and MDD, but much weaker evidence for a relationship between BPD and bipolar disorder [50, 51].

Examination of the effect that the bipolar disorders had on the course of BPD in the CLPS yielded mostly insignificant results, but with one exception: bipolar II significantly increased time to remission of BPD. That bipolar II had this effect, whereas the presumably more severe bipolar I had a lesser effect, is surprising. A possible explanation is that many patients diagnosed as bipolar II may actually have a variation of BPD. This possibility is suggested by bipolar II's relatively weak

familial relationship to bipolar I [51, 52] and by its weak and inconsistent response to mood stabilizers [53]. It is also suggested by bipolar II's high prevalence of typical BPD characteristics such as rejection sensitivity [54], childhood trauma [2], and repeated suicide attempts [55, 56]. Thus, what is commonly identified as co-occurrence of bipolar II with BPD may really be an indication of a more severe form of BPD and it is this level of severity that accounts for the longer time to BPD remission. Examination of the effect of BPD on the time to remission of bipolar disorder or time to relapse/onsets revealed no significant effects. This finding supports the overall conclusion drawn from a prior CLPS report about the independence of these disorders [38]. Though the findings of independence are based on new evidence, this conclusion must be considered with caution because the analyses involving bipolar disorders had significantly smaller samples than for MDD.

The implications of this conceptualization for the DSM suggest certain directions. First is the recognition and further delineation of common personality trait dimensions that underlie both personality disorders and mood disorders. It may further be important to identify individuals who experience episodes of mood disorders, such as major depression, who do not share an ongoing propensity toward negative affectivity. It is possible that the etiology of such episodes is different from those that represent an exacerbation of a persistent temperamental trait. For the personality disorders, it will be important to more clearly define the multiple underlying trait dimensions, including those that are and are not shared with mood disorders. Much work in this direction has already been accomplished, and much has been written regarding the relevance of various dimensional schemes for conceptualizing the personality disorders. Currently, such dimensions are assessed by self-report measures, such as the NEO-Personality Inventory Revised (NEO-PI-R) for the Five-Factor Model of Personality [57], the Dimensional Assessment of Personality Pathology (DAPP) for dimensions of personality disorder [58], the Schedule for Nonadaptive and Adaptive Personality (SNAP) for dimensions of normal and abnormal personality [59], and the Personality Inventory for DSM-5 (PID-5) for the recently published DSM-5 Alternative Model for personality disorders [60]. The ability to assess such dimensions by clinical interview, with additional consideration of the range and examples of behaviors that may be manifestations of the dimensions, will be important to establish the clinical relevance of the dimensions underlying the maladaptive traits and behaviors of personality disorders. With clearer descriptions of the traits underlying the personality disorders, including definitions and assessments that consider the range of possible manifestations of such traits, it will also be important to clarify what is distinctive about personality disorders, to aid in their differential diagnosis from mood and other mental disorders. The DSM-5 Personality and Personality Disorders Work Group developed a model of personality functioning based on impairments in self-concept and incapacities in interpersonal relationships [44]. Impairments in self (identity, self-direction) and interpersonal (empathy, intimacy) functioning appear to be central to BPD, as conceptualized from many different theoretical perspectives [61], as well as to other DSM personality disorder types [62–64].

Finally, will the initial longitudinal relationships linking pathological traits, personality disorders, and other symptoms of psychopathology hold up over time? Such relationships point strongly toward shared endophenotypes, whose identification is critical for genetic studies, treatment development, and classification [65].

Clinical Implications

Personality psychopathology, particularly BPD, should be assessed in all patients with MDD, considered in prognosis, and addressed in treatment. Furthermore, the clinical implications of the findings of the studies reviewed in this chapter include informing patients that the co-occurrence of BPD and MDD can have a negative effect on their prognoses. The response of MDD to antidepressants in the presence of BPD is weak and inconsistent [66, 67]. Thus, the use of antidepressant medications should be restricted to more severe MDD with appropriate cautions about expectable benefits. Treatment of BPD, primarily psychodynamic or cognitive psychotherapy [9–11], should uniformly be offered and given priority; improvement in BPD will be typically followed by improvement in MDD. With respect to co-occurring BPD and bipolar disorders, patients should be treated as if these were independent disorders. Clinical experience suggests that control of mania and hypomania with mood stabilizers or other psychotropic medications often facilitates the use of psychosocial treatments for patients with BPD.

References

1. Ruggero CJ, Zimmerman M, Chelminski I, Young D. Borderline personality disorder and the misdiagnosis of bipolar disorder. J Psychiatr Res. 2010;44:405–8.
2. Zimmerman M, Ruggero CJ, Chelminski I, Young D. Psychiatric diagnoses in patients previously diagnosed with bipolar disorder. J Clin Psychiatry. 2010;71:26–31.
3. Benazzi F. Bipolar II, disorder: epidemiology, diagnosis, and management. CNS Drugs. 2007;21:727–40.
4. Akiskal HS, Bourgeois ML, Angst J, Post R, Moller H, Hirschfield R. Re-evaluating the prevalence of and diagnostic composition within the broad clinical spectrum of bipolar disorders. J Affect Disord. 2000;59 Suppl 1:S5–30.
5. Akiskal HS, Pinto O. The evolving bipolar spectrum: prototypes I, II, III, and IV. Psychiatr Clin North Am. 1999;22:517–34.
6. Judd LL, Akiskal HS, Maser JD, Zeller PJ, Endicott J, Coryell W, et al. A prospective 12-year study of subsyndromal and syndromal depressive symptoms in unipolar major depressive disorders. Arch Gen Psychiatry. 1998;55:694–700.
7. Zimmerman M. Would broadening the diagnostic criteria for bipolar disorder do more harm than good? Implications from longitudinal studies of subthreshold conditions. J Clin Psychiatry. 2012;73:437–43.
8. Skodol AE, Stout RL, McGlashan TH, Grilo CM, Gunderson JG, Shea MT, et al. Co-occurrence of mood and personality disorders: a report from the Collaborative Longitudinal Personality Disorders Study (CLPS). Depress Anxiety. 1999;10:175–82.

9. Leichsenring F, Leibing E. The effectiveness of psychodynamic therapy and cognitive behavior therapy in the treatment of personality disorders: a meta-analysis. Am J Psychiatry. 2003;160:1223–32.
10. Leichsenring F, Rabung S. Effectiveness of long-term psychodynamic psychotherapy: a meta-analysis. JAMA. 2008;300:1551–65.
11. Matusiewicz AK, Hopwood CJ, Banducci AN, Lejuez CW. The effectiveness of cognitive behavioral therapy for personality disorders. Psychiatr Clin North Am. 2010;33:657–85.
12. Gunderson JG, Shea MT, Skodol AE, McGlashan TH, Morey LC, Stout RL, et al. The Collaborative Longitudinal Personality Disorders Study. I: development, aims, design, and sample characteristics. J Pers Disord. 2000;14:300–15.
13. Skodol AE, Shea MT, McGlashan TH, Gunderson JG, Morey LC, Sanislow CA, et al. The Collaborative Longitudinal Personality Disorders Study (CLPS): overview and implications. J Pers Disord. 2005;19:487–504.
14. Zanarini MC, Frankenburg FR, Hennen J, Reich DB, Silk KR. The McLean study of adult development (MSAD): overview and implications of the first six years of prospective follow-up. J Pers Disord. 2005;19:505–23.
15. Grant BF, Stinson FS, Dawson DA, Chou SP, Ruan WJ, Pickering RP. Prevalence and co-occurrence of 12-month alcohol and drug use disorders and personality disorders in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Arch Gen Psychiatry. 2004;61:361–8.
16. Grant BF, Goldstein RB, Chou SP, Huang B, Stinson FS, Dawson DA, et al. Sociodemographic and psychopathologic predictors of first incidence of DSM-IV substance use, mood and anxiety disorders: results from the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions. Mol Psychiatry. 2009;14:1051–66.
17. Cohen P, Crawford TN, Johnson JG, Kasen S. The children in the community study of developmental course of personality disorder. J Pers Disord. 2005;19:466–86.
18. Zanarini MC, Frankenburg FR, Sickel AE, Yong L. The diagnostic interview for DSM-IV personality disorders (DIPD-IV). Belmont: McLean Hospital; 1996.
19. First MB, Gibbon M, Spitzer RL, Williams JBW. Structured clinical interview for DSM-IV Axis I disorders – patient version (SCID-I/P). New York: Biometrics Research Department, New York State Psychiatric Institute; 1996.
20. Keller MB, Lavori PW, Friedman B, Nielsen E, Endicott J, McDonald-Scott P, et al. The Longitudinal Interval Follow-up Evaluation: a comprehensive method for assessing outcome in prospective longitudinal studies. Arch Gen Psychiatry. 1987;44:540–8.
21. Katz MM, Klerman GL. Introduction: overview of the clinical studies program. Am J Psychiatry. 1979;136:49–51.
22. Zanarini MC, Gunderson JG, Frankenburg FR, Chauncey DL. The Revised Diagnostic Interview for Borderlines: discriminating BPD from other Axis II disorders. J Pers Disord. 1989;3:10–8.
23. Grant BF, Dawson DA, Hasin DS. The alcohol use disorder and associated disabilities interview schedule—DSM-IV version (AUDADIS-IV). 2009.
24. Grilo CM, Sanislow CA, Shea MT, Skodol AE, Stout RL, Gunderson JG, et al. Two-year prospective naturalistic study of remission from major depressive disorder as a function of personality disorder comorbidity. J Consult Clin Psychol. 2005;73:78–85.
25. Grilo CM, Stout RL, Markowitz JC, Sanislow CA, Ansell EB, Skodol AE, et al. Personality disorders predict relapse after remission from an episode of major depressive disorder: a six-year prospective study. J Clin Psychiatry. 2010;71:1629–35.
26. Markowitz JC, Skodol AE, Petkova E, Xie H, Hellerstein DJ, Gunderson JG, et al. Longitudinal comparison of depressive personality disorder and dysthymic disorder. Compr Psychiatry. 2005;46:239–45.
27. Gunderson JG, Stout RL, Sanislow CA, Shea MT, McGlashan TH, Zanarini MC, et al. New episodes and new onsets of major depression in borderline and other personality disorders. J Affect Disord. 2008;111:40–5.

28. Gunderson JG, Stout RL, McGlashan TH, Shea MT, Morey LC, Grilo CM, et al. Ten year course of borderline personality disorder: psychopathology and function from the Collaborative Longitudinal Personality Disorders Study. Arch Gen Psychiatry. 2011;68:827–37.
29. Zanarini MC, Frankenburg FR, Hennen J, Reich DB, Silk KR. Axis I comorbidity of borderline personality disorder: description of six-year course and prediction of time-to-remission. Am J Psychiatry. 2004;161:2108–14.
30. Cohen P, Cohen J. The clinician's illusion. Arch Gen Psychiatry. 1984;41:1178–82.
31. Skodol AE, Grilo CM, Keyes KM, Geier T, Grant BF, Hasin DS. Relationship of personality disorders to the course of major depressive disorder in a nationally representative sample. Am J Psychiatry. 2011;168:257–64.
32. Johnson JG, Cohen P, Kasen S, Brook JS. Personality disorder traits associated with risk for unipolar depression during middle adulthood. Psychiatry Res. 2005;136:113–21.
33. Johnson JG, Cohen P, Kasen S, Brook JS. Personality disorders evident by early adulthood and risk for eating and weight problems during middle adulthood. Int J Eat Disord. 2006;39: 184–92.
34. Johnson JG, Cohen P, Kasen S, Brook JS. Personality disorder traits evident by early adulthood and risk for anxiety disorders during middle adulthood. J Anxiety Disord. 2006;20: 408–26.
35. Johnson JG, Cohen P, Skodol A, Oldham JM, Kasen S, Brook JS. Personality disorders in adolescence and risk of major mental disorders and suicidality during adulthood. Arch Gen Psychiatry. 1999;56:805–11.
36. Kasen S, Cohen P, Skodol AE, Johnson JG, Brook JS. Influence of child and adolescent psychiatric disorders on young adult personality disorder. Am J Psychiatry. 1999;156:1529–35.
37. Kasen S, Cohen P, Skodol AE, Johnson JG, Smailes E, Brook JS. Childhood depression and adult personality disorder: alternative pathways of continuity. Arch Gen Psychiatry. 2001;58: 231–6.
38. Gunderson JG, Weinberg I, Kueppenbender KD, Daversa M, Zanarini MC, Shea MT, et al. Descriptive and longitudinal observations on the relationship of borderline personality disorder (BPD) and bipolar disorders. Am J Psychiatry. 2006;163:1173–8.
39. Gunderson JG, Stout RL, Shea MT, Keuroghlian AS, Morey LC, Grilo CM, et al. Interactions of borderline personality disorder and mood disorders over ten years. J Clin Psychiatry. In press.
40. Siever LJ, Davis KL. A psychobiological perspective on the personality disorders. Am J Psychiatry. 1991;148:1647–58.
41. Widiger TA. Personality and depression: assessment issues. In: Klein MH, Kupfer DJ, editors. Personality and depression: a current view, Mental health and psychopathology. New York: Guilford Press; 1993. p. 77–118.
42. McCrae RR, Costa PT. A five-factor theory of personality. In: Pervin LA, John OP, editors. Handbook of personality. Theory and research. 2nd ed. New York: Guilford; 1999. p. 139–53.
43. Clark LA, Watson D, Mineka S. Temperament, personality, and the mood and anxiety disorders. J Abnorm Psychol. 1994;103:103–16.
44. Skodol AE, Krueger RK, Bender DS, Morey LC, Clark LA, Bell CC, et al. Personality disorders in DSM-5 Section III. Focus. 2013;11:187–203.
45. Watson D, Walker LM. The long-term stability and predictive validity of trait measures of affect. J Pers Soc Psychol. 1996;70:567–77.
46. Shea MT, Stout RL, Yen S, Pagano ME, Skodol AE, Morey LC, et al. Associations in the course of personality disorders and axis I disorders over time. J Abnorm Psychol. 2004; 113:499–508.
47. Gunderson JG, Morey LC, Stout RL, Skodol AE, Shea MT, McGlashan TH, et al. Major depressive disorder and borderline personality disorder revisited: longitudinal interactions. J Clin Psychiatry. 2004;65:1049–56.
48. Gunderson JG, Daversa MT, Grilo CM, McGlashan TH, Zanarini MC, Shea MT, et al. Predictors of 2-year outcome for patients with borderline personality disorder. Am J Psychiatry. 2006;163:822–6.

49. Shea MT, Stout RL, Gunderson JG, Morey LC, Grilo CM, McGlashan TH, et al. Short-term diagnostic stability of schizotypal, borderline, avoidant, and obsessive compulsive personality disorders. Am J Psychiatry. 2002;159:2036–41.
50. White CN, Gunderson JG, Zanarini MC, Hudson JI. Family studies of borderline personality disorder: a review. Harv Rev Psychiatry. 2003;11:8–19.
51. Zanarini MC, Barison LK, Frankenburg FR, Reich DB, Hudson JI. Family history study of the familial coaggregation of borderline personality disorder with axis I and nonborderline dramatic cluster axis II disorders. J Pers Disord. 2009;8:357–69.
52. Coryell W, Endicott J, Reich T, Andreasen N, Keller M. A family study of bipolar II disorder. Br J Psychiatry. 1984;145:49–54.
53. Hadjipavlou G, Mok H, Yatham LN. Pharmacotherapy of bipolar II disorder: a critical review of current evidence. Bipolar Disord. 2004;6:14–25.
54. Benazzi F. Exploring aspects of DSM-IV interpersonal sensitivity in bipolar II. J Affect Disord. 2000;60:43–6.
55. Neves FS, Malloy-Diniz LF, Correa H. Suicidal behavior in bipolar disorder: what is the influence of psychiatric comorbidities. J Clin Psychiatry. 2009;70:13–8.
56. Tondo I, Lepri B, Baldessarini RJ. Suicidal risks among 2826 Sardinian major affective disorder patients. Acta Psychiatr Scand. 2007;116:395–402.
57. Costa PT, McCrae RR. Stability and change in personality assessment: the revised NEO personality inventory in the year 2000. J Pers Assess. 1997;68:86–94.
58. Livesley WJ, Jackson DN, Schroeder ML. A study of the factorial structure of personality pathology. J Pers Disord. 1989;3:292–306.
59. Clark LA. Manual for the schedule for nonadaptive and adaptive personality. Minneapolis: University of Minnesota Press; 1993.
60. Krueger RF, Derringer J, Markon KE, Watson D, Skodol AE. Initial construction of a maladaptive personality trait model and inventory for DSM-5. Psychol Med. 2012;42:1879–90.
61. Bender DS, Skodol AE. Borderline personality as a self-other representational disturbance. J Pers Disord. 2007;21:500–17.
62. Bender DS, Morey LC, Skodol AE. Toward a model for assessing level of personality functioning in DSM-5, part I: a review of theory and methods. J Pers Assess. 2011;93:332–46.
63. Morey LC, Berghuis H, Bender DS, Verheul R, Krueger RF, Skodol AE. Toward a model for assessing level of personality functioning in DSM-5, part II: empirical articulation of a core dimension of personality pathology. J Pers Assess. 2011;93:347–53.
64. Morey LC, Bender DS, Skodol AE. Validating the proposed DSM-5 severity indicator for personality disorder. J Nerv Ment Dis. 2013;201:729–35.
65. Skodol AE, Shea MT, Yen S, White CN, Gunderson JG. Personality disorders and mood disorders: perspectives on diagnosis and classification from studies of longitudinal course and familial association. J Pers Disord. 2010;24:83–108.
66. Soloff PH, George A, Nathan S, Schulz PM, Cornelius JR, Herring J, et al. Amitriptyline versus haloperidol in borderlines: final outcomes and predictors of response. J Clin Psychopharmacol. 1989;9:238–46.
67. Feurino L, Silk KR. State of the art in the pharmacologic treatment of borderline personality disorder. Curr Psychiatry Rep. 2011;13:69–75.

Part V
Treatment

Chapter 11
Pharmacology

Kenneth R. Silk

Introduction

The pharmacologic treatment of depression in borderline personality disorder (BPD) in many respects has changed over the years. These changes reflect (a) trends in understanding where BPD lies or was thought to lie in the diagnostic schema and its possible relationship to near neighbor axis I disorders (though in DSM-5 there no longer is an axis I and an axis II), (b) a better appreciation of what has been viewed as "depression" in BPD and distinguishing that from a major depressive episode which can exist as a comorbid condition in BPD, and (c) trends in psychopharmacologic treatment of psychiatric disorders in general and how those trends are reflected in the suggested pharmacologic treatment of depression in BPD and of BPD. The phrase "suggested pharmacologic treatment" is used intentionally since as of this writing there is still no medication or medication class that has received approval or indication for treatment of patients with BPD.

This chapter will briefly review points (a) and (b) above because they are covered in much more detail in the rest of this book. Nonetheless, they will be mentioned in order to set the scene for the focus of this chapter, the pharmacologic treatment of depression in BPD. More detail will be presented with regard to (c) above. The chapter will then discuss how one might proceed with pharmacologic treatment (if so chosen) in patients with BPD who are also reporting depression or depressive affect, dysphoria or dysthymia. It will also review pharmacologic treatment for mood instability. The chapter will address the competing positions of those who believe there is no role for pharmacology in BPD except in certain acute situations and then for only a short time versus those who believe that despite having little consistent solid evidence as to the effectiveness of any class of psychotropic

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medications in this patient population, there is some benefit to the judicious use of medications here, even if its use is merely to diminish the "noise" and lability of the system so that the patient may have a better chance of making use of psychosocial treatments. It is of interest that in the last 20 years while there have been a number of psychosocial treatments for BPD that have been shown to be effective in randomized control trials (RCTs) though there may not be consistency as to which type of psychosocial or psychotherapeutic treatment is most effective for any given symptom or symptom complex in any particular individual. Similar progress has not been made in the pharmacologic treatment of BPD.

BPD on the Diagnostic Continuum

BPD's Relation to Psychosis

In considering the specific pharmacologic treatment recommended via clinical trials, by expert panels, or published guidelines for patients with BPD, attention should be drawn to the issue that the medications or the medication classes suggested and utilized appear to have changed every 10–15 years. Those differences are most probably related to how BPD was thought of as a psychiatric disorder. Up until the late 1960s or mid-1970s, BPD was often thought of primarily as a disorder closely related to psychosis [1–5]. While BPD was usually not viewed in the same way as a "true" psychosis, it was clear that some people with BPD took at least short dips into psychosis or psychotic-like thinking. The psychosis almost by definition was never long-lasting and appeared to be related to stress [6–8]. It was also felt that these patients while temporarily losing their relationship to reality, never really lost their ability to test reality [9]. In other words, these patients did not in general form permanent delusional explanations for their distortions of reality, and in fact the loss of their relationship to reality was often an ego-dystonic phenomenon causing them substantial anxiety. This loss of or distortion in relationship to reality could take the form of transient auditory hallucinations of a few words being repeated or unintelligible sounds, or paranoid ideation or dissociation [8, 10]. In this context one can appreciate why in the late 1970s to the mid-1980s antipsychotic medications were often recommended as the pharmacologic class to be used in these patients with BPD [11, 12] even when the borderline patient was thought to be suffering from depression [13].

The close relationship of BPD to psychosis was not an idea that would have permanence though the ninth criterion in the DSM-5 criteria set for BPD still remains "transient, stress-related paranoid ideation or severe dissociative symptoms" [14]. In the proposed, but eventually rejected, dimensional model for DSM-5, this concept would fall under the trait domain of psychoticism (cognitive and perceptual dysregulation), but the domain of psychoticism is not listed or captured in the BPD criteria set in the proposed alternate DSM-5 model [14], found in Section 3 of

DSM-5. Rather, in the mid- to late 1970s when BPD was beginning to be accepted as a legitimate diagnostic entity by at least some psychiatrists, the diagnosis's relationship to mood disorders and to affective dysregulation was thought of as a more probable association than a relationship to psychosis.

BPD's Relation to Mood

Since the time that Schmideberg [15] implied that much of the change in mood and other mental states often seen in patients who would eventually be labeled with BPD as more of a stable way of behaving (leading to the notion of stable instability), the idea of BPD being more closely related to a mood disorder took hold and has remained a central though not an immutable notion in understanding the psychopathology and clinical presentation of patients with BPD. Kernberg's concept [16] of the patient with borderline personality organization experiencing affects in the areas of anger, aggression, and anxiety and Grinker's delineation of a core borderline group with labile or unstable interpersonal relationships, chronic loneliness, and anger [17] pointed the way to considering affects and their dysregulation rather than cognitive disorganization as the core features of BPD. The idea of BPD as a disorder more closely related to mood disorders became firmly established with Gunderson and Singer's seminal paper, "Defining Borderline Patients" in the *American Journal of Psychiatry* in 1975 [18], in which they emphasized the idea of intense affect, particularly depression and anger, and impulsivity as being among the core features of BPD (though they also continued to emphasize the psychotic-like phenomena that these patients also displayed). This paper and the subsequent work by Gunderson and colleagues led to the incorporation of BPD into DSM-III in 1980 [19]. And while the criteria may have been modified slightly in different versions of the DSM, nonetheless in DSM-5 (essentially a replication of DSM-IV-TR), at least 3 of the 9 criteria can be thought of as having some relationship to mood (recurrent suicidal or parasuicidal behavior, affective instability that includes dysphoria and anxiety, and chronic feelings of emptiness [14]). Further, the close tie that BPD was thought to have in relationship to mood disorders may have been more strongly influenced not by these developments but perhaps by two important papers, the paper by Spitzer et al. [20] that separated off the patients who had been included in the borderline group that were in actuality more closely related to schizophrenia (schizotypal personality disorder) from those with a more unstable personality disorder (borderline personality disorder) and the papers by Akiskal and his colleagues [21, 22] who refuted the separate diagnosis of borderline personality disorder and thought that these patients were really part of the affective spectrum. This somewhat new focus on the possibility of BPD being part of the affective disorder spectrum then fostered the next wave of pharmacologic studies that involved primarily but not exclusively antidepressant medication [13, 23–28]. These studies of antidepressant medications were spurred on by the approval of fluoxetine and other SSRIs for the treatment of

affective disorders and by the profession's wide acceptance of fluoxetine as almost a panacea for everything (except psychosis) that ailed psychiatric patients [29–31]. Fluoxetine and other SSRIs also edged out the attention that was being paid to monoamine oxidase inhibitors that were gaining favor for their use in "atypical depressions," often thought to be closely related to BPD [32]. This initial enthusiasm about the use of SSRIs in BPD faded after the turn of the century probably because of two factors: (a) the somewhat disappointing effect of antidepressants, particularly the SSRIs, in the treatment of BPD as psychosocial interventions were gaining strength and empirical support with regard to their effectiveness and (b) the fact that the patents were running out or had run out on this class of medication and thus there was little financial support to further explore their usefulness in BPD.

Depression in BPD

As clinicians were becoming more dissatisfied with the lack of real effectiveness for the antidepressant medication in BPD, there was also a growing appreciation of the nature of the relationship between BPD and depression. In essence, that is what this book is about, but in general the conclusions were essentially that what is often referred to as depression in BPD is more often than not different from the depression that is usually referred to in psychiatry in general. (One might argue that the word "depression" is overused in psychiatry and the assumption that the use of the word and clinical complaint of depression is equivalent to the idea of major depression is a misunderstanding that needs much more attention, clarification, and refinement.)

The point that needs to be made at this juncture is that it is important to inquire very carefully when a person with BPD states that she is depressed. Too often the assumption is made that the patients are suffering from a major depressive episode, and often they do complain of concomitant sleep disturbance, appetite disturbance, change in energy, negative cognitions, an increase in suicidality or other self-destructive impulses, and a profound sadness and lack of motivation. However, further exploration of these symptoms and the "episode" of illness may reveal that these periods last for less than a week and are often triggered by outside interpersonal events. There is an absence of global anhedonia. These people frequently respond positively to active caring attention from others, so positively that the appropriate interpersonal interaction with the right person can lift them out of their depressed state. They usually do not suffer a loss of libido, but do complain of emptiness and loneliness, affects that clinicians often misinterpret as major depression [17, 33–35]. This delineation and differentiation of BPD from major depression is what this book is about and throughout the years there have been many reviews on this topic [36–38].

What is most important for our purposes in this chapter is an appreciation that there is no medication for loneliness or emptiness, and if we are to consider a medication that might at all temper a person's labile responses to environmental

events, then perhaps we need to turn towards the class of mood stabilizers and/or the class of antipsychotics if we are to expect even a modest clinical response. It may be that patients with BPD who suffer from chronic dysphoria and loneliness and emptiness and complain of these symptoms by labeling them "depression" are being unsuccessfully treated with SSRIs or combinations of antidepressants and other drugs that allegedly augment antidepressant response without success. Then these patients receive the label of "treatment-resistant depression" that affords them the opportunity to receive more aggressive somatic treatment [39]. While the evidence or data supporting this previous statement have yet to be accumulated, caution needs to be taken before we mislabel people with dysphoria secondary to character pathology and failed or strained interpersonal relationships "treatment resistant," since being given simultaneously multiple types of psychotropic medication has more evidence for facilitating side effects and weight gain rather than therapeutic improvement.

What is interesting is that if you ask patients with BPD who expect to be put on antidepressant medication or are seeking another antidepressant medication because of a repeated series of pharmacologic failures, would they prefer to be put on a new antidepressant medication or would they prefer to be on a medication that may smooth out their mood and make them less reactive to environmental stimulation/provocation, they will almost always choose the medication that will help decrease their reactivity. In the course of that discussion, these patients begin to recognize that depression is only one of the reactions or emotions (in addition to anger, irritability, anxiety, etc.) that they experience. This is an important discussion to have because it can lead to an understanding of why antidepressants have failed to be effective, i.e., the problem is not one of having depressions but rather one of being prone to (over)react too strongly when only one of those reactions involves the experience of affect interpreted as depression. What these patients need and what they often are actually seeking is relief from the constant shifting of their moods, moods that even they cannot predict. In actuality, these patients are seeking better regulation of their chronic dysregulation of mood, the now famous emotion dysregulation that is thought to be at the core of many BPD patients interpersonal and affective difficulties [40]. A discussion of this difference between mood (over) reactivity, mood lability, and depression sets the stage for more realistic expectations on the part of both patient and prescriber as to what can actually be expected from psychopharmacologic agents and what to look for in evaluating their effectiveness. A truly comprehensive discussion of this issue would involve a discussion of the diagnosis of BPD [41].

Trends in Class Choice in Prescribing Pharmacologic Agents

Another factor impacting the continuing use of antidepressants despite a reasonable conclusion from a number of systematic and Cochrane reviews to the contrary is that the American Psychiatric Association's (APA) *Practice Guidelines for the*

Treatment of Patients with Borderline Personality Disorder [42] recommends the use of SSRIs for many affective symptoms and emotional dysregulation experiences including impulsive aggression, anger, mood lability, rejection sensitivity, "mood crashes," temper outbursts, and self-damaging and often impulsive acts. The APA Guidelines were based on the careful work of Paul Soloff. His work took place during the late 1980s and 1990s when SSRIs were believed to be a very effective pharmacologic intervention for all types of psychiatric ailments [29–31, 43]. Soloff based his algorithm on all available data and at the time, did not restrict his supporting data to placebo-controlled double-blind RCTs. He "ranked" the importance of the studies by the evidence of efficacy supported through empirical research, then by safety, and then by rapidity of action. He also assumed that the use of the medications would be in an outpatient setting [43]. But among all the studies that he considered, there were only 7 placebo-controlled double-blind RCTs. Six of those 7 involved an antidepressant as one of the drug classes studied [13, 23, 24, 26, 28, 44]; four of the 7 studies included an antipsychotic medication [11–13, 44]; and two of the 7 had a mood stabilizer among the studied drugs [44, 45]. The totals add up to more than 7 medications because some had more than one medication class in the trial.

The mood stabilizers and the antipsychotics, particularly the atypical antipsychotic medications, were to play an increasing role not only in trials with patients with BPD but in trials across a wide range of psychiatric diagnoses. Atypical antipsychotic medications have been promoted for treatment-resistant depression as well as bipolar depression [46, 47], and the practice is in wide use despite contradictory evidence for its effectiveness [48]. Both classes of medications have been used in bipolar disorder, in situations of tempering current manic episodes as well as prophylaxis against future episodes and as interventions to mollify emotional instability [49, 50].

A fuller appreciation of the role that antidepressants and mood stabilizers have begun to play in the pharmacologic treatment of BPD may come from understanding that since 1998, there have been 15 placebo-controlled trials of medications in people with BPD that have regularly been cited in systematic reviews and meta-analyses in addition to the seven that were included in the development of the algorithm by Soloff and the APA. Seven of those trials involved mood stabilizers [51–57] and the mood stabilizers considered involve valproate and topiramate, five involved atypical antipsychotic medications [58–62] and the antipsychotics considered involve olanzapine, aripiprazole, and ziprasidone, while only two involved SSRIs [25, 63] and they were fluvoxamine and fluoxetine. One additional trial involved a combination of an SSRI and an atypical antipsychotic [64]. One of the SSRIs trials was a study of the effectiveness of fluoxetine in augmenting dialectical behavior therapy (DBT [63]), and one of the atypical antipsychotic trials was a study of the effectiveness of olanzapine in augmenting DBT [62].

As we consider how best to treat pharmacologically the depression that is found in BPD, aside from the BPD patient who is also currently comorbid for a major depressive episode [65], we must realize that antipsychotics and mood stabilizers are currently very heavily promoted for the treatment of all types of psychiatric illnesses.

Drugs that are members of these two classes of medication are only recently coming off "patent," and clinical trial research into their effectiveness across a wide range of disorders is still very active. It is not surprising now that these medication classes seem to be the classes that have garnered the most evidence for treatment of a wide array of symptoms in BPD [66, 67], but the evidence that appears to support their use may reflect more about the frequency with which these medications are subjected to clinical trials rather than any valid increase in effectiveness of one drug or one class of drugs over another in BPD. It should be remembered that when the APA Guidelines were published in 2001, they recommended SSRIs for a wide array of symptoms in BPD, and over time, those recommendations may have been more of a reflection of the frequency with which those medications were subjected to empirical trials and not a true representation of the effectiveness of these medications in BPD.

Choosing a Pharmacologic Agent for Mood Disturbance in BPD

A few points need to be established at this juncture. The first is that there is not universal agreement that medications should be used in BPD. The APA Guidelines expressed modest caution as to what could be expected when using pharmacologic agents in patients with BPD when they said:

> "Pharmacotherapy often has an important adjunctive role, especially for diminution of targeted symptoms such as affective instability, impulsivity, psychotic-like symptoms, and self-destructive behavior. However, pharmacotherapy is unlikely to have substantial effects on some interpersonal problems and some other features of the disorder… Clinical experience indicates that many patients will benefit most from a combination of psychotherapy and psychopharmacology" [42].

The NICE guidelines from the National Institute for Health and Clinical Excellence in the United Kingdom took a bolder position when it stated:

> "Drug treatment should not be used specifically for borderline personality disorder or for the individual symptoms or behaviour associated with the disorder (for example, repeated self-harm, marked emotional instability, risk-taking behaviour and transient psychotic symptoms)" [68].

An early Cochrane review [69] found mixed and not very convincing evidence for the pharmacologic treatment of depression in patients with BPD. It concluded that "If offered medication, people with BPD should know that this is not based on good evidence from trials. That does not mean it may not do considerable good and there is no indication of significant harm. People with BPD or their caregivers are in a position to lobby for and facilitate good research in this area" [69].

One of the most insistent people warning us against the overreach of psychopharmacologic treatment in patients with BPD is Joel Paris from McGill in Montreal. Paris writes: "We can prescribe antipsychotics, but patients with BPD do not have true psychosis. We can prescribe antidepressants, but patients with BPD do not have

classic depression. We can prescribe mood stabilizers, but the affective instability is not the same as the symptoms of bipolar disorder" [70]. The psychopharmacologic management of BPD organizes itself around its approximation of discrete overt symptoms seen in other psychiatric conditions, rather than its underlying core vulnerabilities or the specific phenomenology of its manifest presentation. Therefore, treatment with medication is not in itself definitive or coherent.

A more recent Cochrane review of pharmacotherapy in BPD [71] came to somewhat different conclusions from the Binks et al. review. Lieb et al. added 15 additional studies to the 10 studies included in Binks et al. [69], and they concluded that there was no evidence for pharmacologic effectiveness for the symptoms of abandonment or emptiness, symptoms often mistaken for depression in patients with BPD; that there was no evidence for SSRI effectiveness when the patient was not in a concurrent major affective episode; that there was some evidence for the effectiveness of mood stabilizers along with antipsychotics for affective dysregulation; and that there was some evidence for the effectiveness of mood stabilizers for impulsivity and anger [71], behaviors that have often been referred to in these patients as impulsive aggression.

The antidepressants that have been systematically studied in BPD include mianserin [24], tranylcypromine [44], phenelzine [28], amitriptyline [27], fluoxetine [23, 26, 63], and fluvoxamine [25, 72]. Despite these various antidepressants being used, no one antidepressant stands out as particularly effective for diminishing the depression that is not part of a major depressive episode in people with BPD. Further, in examining across the studies that used the same antidepressant, in this case fluoxetine which was the studied SSRI in 3 reports [23, 26, 63], in only one of those 3 studies [26] was fluoxetine seen as more effective than placebo for "depression." One other study involved the SSRI fluvoxamine [25], and that study did not report improvement over placebo with respect to a reduction in depression but it did report some benefit for rapidly shifting moods, a symptom not measured in the other studies involving SSRIs.

One of the difficulties we face at this time is that these studies of antidepressants do not use the same medication, do not evaluate the same outcome measures, and, if they do employ the same measures, they do not across studies necessarily use the same instruments to asses those outcomes. Thus, results become contradictory and there is little guidance in how to interpret or understand the results from one study to another.

In exploring the impact of the antipsychotic medications (primarily but not exclusively the atypicals), one encounters the same dilemmas. For example in one [73], thiothixene was found to reduce depressive affect, but in another study [11], it was specifically mentioned that thiothixene did not improve depression any more than placebo. A similar problem occurs when examining the role of olanzapine, the most studied of the atypical antipsychotics in patients with BPD. In two studies it was shown to reduce anxiety [62, 74], but a third study specifically noted that it did not reduce anxiety [58]. In a similar fashion olanzapine was thought to reduce aggression over placebo in two [62, 74] of 4 studies. In only one study was it noted to reduce depression [62]. The studies that involve antipsychotic medications then suffer from the same methodological problems that plague the studies involving antidepressants [75].

How might we then make a rational decision as to which medication to prescribe for mood or mood disturbances in these patients? In a review by Silk and Feurino III [76], seven meta-analyses or systematic reviews of randomized controlled trials of pharmacotherapy of BPD were examined. Because of the differences in outcomes that were measured across the various studies and because the instruments used to measure that outcome differed, they attempted to cluster outcome into the four main dimensions of what Siever and Davis [77] suggested were biologically supported domains that could be applied across the different personality disorders: (a) affective instability, (b) impulsivity/aggression, (c) cognitive–perceptual disturbances, and (d) anxiety/inhibition. Clinical variables that different RCTs defined as their outcome measures were sorted into one of those four categories. The first two categories/dimensions, affective instability and impulsivity/aggression, will be reviewed here. Affective instability includes emotional dysregulation and depression. Impulsivity/aggression can reflect a dimension found in many mood disorders [67]. Listed under "affective instability" were abandonment, affective instability, capacity for pleasure, depression, emptiness, euphoria/mania, identify disturbance, interpersonal sensitivity, irritability, rejection sensitivity, and suicidality, while listed under "impulsivity/aggression" were aggression, anger, hostility, and impulsiveness. The symptom of suicidality could just as readily fit under impulsivity/aggression as it does under affective instability, and the symptom of anger could just as readily be placed under affective instability as it does under impulsivity/aggression.

Each of the 7 systematic reviews or meta-analyses was appraised to determine which class of psychotropic medication did each suggest might have some effectiveness in each of the aforementioned dimensions. The studies reviewed were by Binks et al. [69], Duggan et al. [78], Herpertz et al. [79], Ingenhoven et al. [80], Lieb et al. [71], Mercer et al. [81], and Nosè et al. [82].

While there was not universal agreement as to which drugs or classes of drugs were most effective in the dimensions of affective instability and impulsivity/aggression, there were distinct trends. Four of the 7 reviews favored the use of mood stabilizers for affective instability [71, 80–82]. Nosè et al. [82] felt that there was some data to support also the use of antidepressants, particularly SSRIs in this dimension, and Binks et al. [69] found some weak evidence for antidepressants here. Mercer et al. [81] found some effectiveness for the antipsychotic medications, but their effectiveness was not better than the effectiveness of mood stabilizers, and Lieb et al. [71] found some weak role for the mood stabilizers here as well. But two points need to be made. Firstly, there was little data to support the use of antidepressants except in the World Federation of Biological Psychiatry Guidelines for Biological Treatment of Personality Disorders [79], and the support is for when the patient was in an actual major depressive episode. There was little support for the treatment of depression when it was not part of a major depressive episode in any of the other reviews save some very weak support by Binks et al. [69] who only reviewed 10 studies, while most of the other reviews had at least 20 studies that were evaluated. Mercer et al. [81] had only 18 studies in their review, but they were looking only at the outcome symptoms of depression and anger. And while Mercer's

group was specifically looking at depression as an outcome, they found that antidepressants had only a small effect size on depression, while there were medium effect sizes for depression for both the antipsychotics and the mood stabilizers. Secondly, in the realm of affective dysregulation that includes, but is not limited to, the symptom of depression, the majority of the data and evidence supported the use of mood stabilizers. Yet even when there was support for the use of a given medication or class of medications in this dimension, the support was quite modest.

In the dimension of impulsivity/aggression, most of the support was for use of mood stabilizers followed by the antipsychotic medications. Five of the seven studies found mood stabilizers to have the most effectiveness here [71, 78–81], though Herpertz et al. [79] and Ingenhoven et al. [80] found antipsychotic medication to be equally as effective. Lieb et al. [71] observed that antipsychotics had some effectiveness as well but not as much as the mood stabilizers, and Nosè et al. [82] supported the class of antipsychotic medications as effective with little evidence for mood stabilizers. So while there is the most support for the use of mood stabilizers in this dimension, there is also substantial support for the use of antipsychotic medication.

But these two different classes of medications are not equivalent when you consider their side effects. On the one hand the mood stabilizers appear in general to cause less, but certainly not in some instances insubstantial, weight gain, a problem with the antipsychotics [83]. The mood stabilizers also carries risk of Stevens–Johnson syndrome (not limited to lamotrigine but certainly thought to be the drug that is the most dangerous [84]). Yet the atypical antipsychotics appear to enhance the chances of developing a metabolic syndrome. It is of note that these medications are often used in a patient population that is female and of child-bearing age and potential, and as a broad category, the mood stabilizers are significantly more teratogenic than the atypical antipsychotics [85, 86]. In addition, this is not a population that would experience improved self-esteem if there was also substantial weight gain.

In summary, we might ask which of any of these medications might be effective in the "depressions" found in BPD. In the presence of a comorbid major depressive episode, there is good evidence for the use of SSRIs for the major depressive episode but not necessarily for the other depressions that coexist in patients with BPD. And yet there is some evidence that improvements in the BPD may have more influence on the ultimate improvement in the major depression than vice versa [87].

If one wishes to include the idea of mood instability as part of the "depression" found in BPD, then there is some evidence from RCTs for the use of lamotrigine, or valproate, or topiramate among the mood stabilizers, as well as some evidence for the use of aripiprazole, or ziprasidone, or perhaps olanzapine among the antipsychotic medications. But one must use caution because the evidence is not always consistent, the N's have been small in most studies, and too often there has not been replication of positive findings from different groups of researchers [88]. Further, the side effect profile of each of these classes of drugs needs to be considered when trying to choose between one class and another class or between specific medications within the class. There is no evidence that using a medication from each of these classes has any increased benefits but they can increase the side effect risk.

Managing the Prescribing of Medications

Even when we examine the best data, we find many inconsistencies, and the guidance we have with respect to the pharmacologic treatment of depression or of mood instability is modest at best (Table 11.1). The results of various studies and different reviews differ despite the fact that most of these meta-analyses looked at the same

Table 11.1 Studies of pharmacologic efficacy in borderline personality disorder

Drug class	Findings	Studies
Antidepressants[a]	Affect instability	Binks et al. [69]
		Herpertz et al. [79]
		Nosè et al. [82]
	Anger	Binks et al. [69]
	Anxiety	Herpertz et al. [79]
Antipsychotics (*Primarily but not exclusively atypicals*)	Affect instability	Lieb et al. [71]
		Mercer et al. [81]
	Anger	Herpertz et al. [79]
		Ingenhoven et al. [80]
		Lieb et al. [71]
		Nosè et al. [82]
	Aggression	Herpertz et al. [79]
		Ingenhoven et al. [80]
		Lieb et al. [71]
		Nosè et al. [82]
	Global functioning (weak evidence)	Binks et al. [69]
		Nosè et al. [82]
	Cognitive perceptual symptoms	Binks et al. [69]
		Duggan et al. [78]
		Herpertz et al. [79]
		Ingenhoven et al. [80]
		Lieb et al. [71]
Mood stabilizers	Affect instability	Ingenhoven et al. [80]
		Lieb et al. [71]
		Mercer et al. [81]
		Nosè et al. [82]
	Anxiety	Ingenhoven et al. [80]
	Impulsivity/aggression	Duggan et al. [78]
	Anger	Herpertz et al. [79]
		Ingenhoven et al. [80]
		Lieb et al. [71]
		Mercer et al. [81]
	Global functioning	Ingenhoven et al. [80]

[a]Most studies agree that antidepressants are only effective for depression when there is a current comorbid major depressive episode

studies of a substantial subset of about 25 identified RCTs. The inconsistency in conclusions most probably reflects not only the weakness of even the best available data but also the small sample sizes in most of the studies and the different outcome variables and different measures to quantify and evaluate those outcomes [67, 88].

Nonetheless, a few guidelines should be mentioned and these are elaborated in more detail elsewhere [89]:

1. There should be a frank discussion of what the patient means when she uses the word depression, and if appropriate, there should be further discussion about how the depression that the patient is suffering differs from that in a major depressive episode. This discussion can address the fact that antidepressant medication effectiveness has been shown in the specific depressive entity of major depressive disorder, but there is little evidence for medication effectiveness in other "depressions." This does not mean that medications or some medication will not be tried and might even turn out to be helpful, but the benefits one might receive will usually be quite modest at best.
2. Elaborating on the point made above, the patient needs to be told that since the research for effectiveness for these drugs reveals modest effect at best, the greatest amount of progress and improvement will come from the psychotherapeutic work. This does not mean that patients will get no benefit from pharmacologic treatment, but they should work towards not idealizing the pharmacology or any particular pharmacologic agent.
3. There is no data that supports the use of polypharmacy, and it is best to treat with one medication, to appreciate the targeted outcome with or for that medication, and, if after the medication has been tried for a sufficient amount of time, to stop that medication before starting another one. There is no evidence for augmentation of medications in BPD.
4. It is important that all these discussions take place an appreciation by the patient that one of the diagnoses being considered is BPD. In fact such discussions should take place at the initiation of psychopharmacologic treatment [41]. The prescriber should not assume that the patient already has this knowledge, as the patient's prior experience may have been with a psychiatrist who believed that the patient had treatment-resistant affective illness and approached treatment from the position that finding the right combination of medications is all that the patient needed in order to improve.

References

1. Deutsch H. Some forms of emotional disturbance and their relationship to schizophrenia. Psychoanal Q. 1942;11:301–21.
2. Hoch P, Polatin P. Pseudoneurotic forms of schizophrenia. Psychiatr Q. 1949;23:248–76.
3. Klein M. Notes on some schizoid mechanisms. Int J Psychoanal. 1946;27:99–110 (Reprinted in J Psychother Prac Res. 1996;5:164–79.).
4. Knight RP. Borderline states. Bull Menninger Clin. 1953;17:139–50.

5. Zilboorg G. Ambulatory schizophrenia. Psychiatry. 1941;4:149–55.
6. Chopra HD, Beatson JA. Psychotic symptoms in borderline personality disorder. Am J Psychiatry. 1986;143:1605–7.
7. Links PS, Steiner M, Mitton J. Characteristics of psychosis in borderline personality disorder. Psychopathology. 1989;22:188–1983.
8. Silk KR, Lohr NE, Westen D, Goodrich S. Psychosis in borderline patients with depression. J Personal Disord. 1989;3:92–100.
9. Frosch J. The psychotic character. Clinical psychiatric considerations. Psychiatr Q. 1964; 38:81–96.
10. Barnow S, Arens EA, Sieswerda S, Dinu-Biringer R, Spitzer C, Lang S. Borderline personality disorder and psychosis: a review. Curr Psychiatry Rep. 2010;12:186–95.
11. Goldberg SC, Schulz SC, Schulz PM, Resnick RJ, Hamer RM, Friedel RO. Borderline and schizotypal personality disorders treated with low-dose thiothixene vs placebo. Arch Gen Psychiatry. 1986;43:680–6.
12. Leone NF. Response of borderline patients to loxapine and chlorpromazine. J Clin Psychiatry. 1982;43:148–50.
13. Soloff PH, George A, Nathan RS, Schulz PM, Ulrich RF, Perel JM. Progress in pharmacotherapy of borderline disorders. A double-blind study of amitriptyline, haloperidol, and placebo. Arch Gen Psychiatry. 1986;43:691–7.
14. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington: American Psychiatric Publishing; 2013.
15. Schmideberg M. The treatment of psychopaths and borderline patients. Am J Psychother. 1947;1:45–70.
16. Kernberg OF. Borderline personality organization. J Am Psychoanal Assoc. 1967;15:641–85.
17. Grinker RR, Werble G, Drye RC. The borderline syndrome. A behavioral study of ego functions. New York: Basic Books; 1968.
18. Gunderson JG, Singer MT. Defining borderline patients, an overview. Am J Psychiatry. 1975;132:1–10.
19. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 3rd ed. Washington, DC: American Psychiatric Association; 1980.
20. Spitzer RL, Endicott J, Gibbon M. Crossing the border into borderline personality and borderline schizophrenia: the development of criteria. Arch Gen Psychiatry. 1979;36:17–24.
21. Akiskal HS, Chen SE, Davis GC, Puzantian VR, Kashgarian M, Bolinger JM. Borderline: an adjective in search of a noun. J Clin Psychiatry. 1985;46:41–8.
22. Akiskal HS, Hirschfeld RMA, Yerevanian BI. The relationship of personality to affective disorders, critical review. Arch Gen Psychiatry. 1983;40:801–10.
23. Coccaro EF, Kavoussi RJ. Fluoxetine and impulsive aggressive behavior in personality-disordered subjects. Arch Gen Psychiatry. 1997;54:1081–8.
24. Montgomery SA, Montgomery D. Pharmacological prevention of suicidal behavior. J Affect Disord. 1982;4:291–8.
25. Rinne T, van den Brink W, Wouters L, van Dyck R. SSRI treatment of borderline personality disorder: a randomized, placebo-controlled clinical trial for female patients with borderline personality disorder. Am J Psychiatry. 2002;159:2048–54.
26. Salzman C, Wolfson AN, Schatzberg A, Looper J, Henke R, Albanese M, et al. Effect of fluoxetine on anger in symptomatic volunteers with borderline personality disorder. J Clin Psychopharmacol. 1995;15:23–9.
27. Soloff PH, George A, Nathan RS, Schulz PM, Cornelius JR, Herring J, et al. Amitriptyline versus haloperidol in borderlines: final outcomes and predictors of response. J Clin Psychopharmacol. 1989;9:238–46.
28. Soloff PH, Cornelius J, George A, Nathan S, Perel JM, Ulrich RF. Efficacy of phenelzine and haloperidol in borderline personality disorder. Arch Gen Psychiatry. 1993;50:377–85.
29. Kramer P. Listening to Prozac. New York: Viking; 1993.
30. Healy D. The antidepressant era. Cambridge: Harvard University Press; 1997.

31. Healy D. Let them eat Prozac. The unhealthy relationship between the pharmaceutical industry and depression. New York: New York University Press; 2004.
32. Parsons B, Quitkin FM, McGrath PJ, Stewart JW, Tricamo E, Ocepek-Welikson K. Phenelzine, imipramine, and placebo in borderline patients meeting criteria for atypical depression. Psychopharmacol Bull. 1989;25:524–34.
33. Gunderson JG. Borderline personality disorder. Washington, DC: American Psychiatric Press; 1984.
34. Silk KR. The quality of depression in borderline personality disorder and the diagnostic process. J Personal Disord. 2010;24:25–37.
35. Westen D, Moses J, Silk KR, Lohr NE, Cohen R, Segal H. Quality of depressive experience in borderline personality disorders: when depression is not just depression. J Personal Disord. 1992;6:382–93.
36. Gold LJ, Silk KR. Exploring the borderline personality disorder-major affective disorder interface. In: Paris J, editor. Borderline personality disorder: etiology and treatment. Washington, DC: American Psychiatric Press; 1993. p. 39–66.
37. Gunderson JG, Phillips KA. A current view of the interface between borderline personality disorder and depression. Am J Psychiatry. 1991;148:967–75.
38. Gunderson JG, Links P. Borderline personality disorder: a clinical guide. 2nd ed. Washington, DC: American Psychiatric Press; 2008.
39. Main TF. The ailment. Br J Med Psychol. 1960;33:29–31.
40. Linehan MM. Cognitive-behavioral treatment of borderline personality disorder. New York: Guilford Press; 1993.
41. LeQuesne ER, Hersh RG. Disclosure of a diagnosis of borderline personality disorder. J Psychiatr Pract. 2004;10:170–6.
42. American Psychiatric Association. Practice guidelines for the treatment of patients with borderline personality disorder. Am J Psychiatry. 2001;158(10, Suppl):S1–52.
43. Soloff PH. Algorithms for pharmacological treatment of personality dimensions: symptom-specific treatments for cognitive-perceptual, affective, and impulsive-behavioral dysregulation. Bull Menninger Clin. 1998;62:195–214.
44. Cowdry RW, Gardner DL. Pharmacotherapy of borderline personality disorder. Alprazolam, carbamazepine, trifluoperazine, and tranylcypromine. Arch Gen Psychiatry. 1988;45:111–9.
45. de la Fuente JM, Lotstra F. A trial of carbamazepine in borderline personality disorder. Euro Neuropsychopharmacol. 1994;4:479–86.
46. Gao K, Calabrese JR. Newer treatment studies for bipolar depression. Bipolar Disord. 2005;7 Suppl 5:13–23.
47. Nemeroff CB. Use of atypical antipsychotics in refractory depression and anxiety. J Clin Psychiatry. 2005;66 suppl 8:13–21.
48. Spielmans GI, Berman MI, Linardatos E, Rosenlicht NZ, Perry A, Tsai AC. Adjunctive atypical antipsychotic treatment for major depressive disorder: a meta-analysis of depression, quality of life, and safety outcomes. PLoS Med. 2013. Available http://dx.doi.org/10.1371/journal.pmed.1001403.
49. Rothchild AJ, editor. The evidence-based guide to antidepressant medications. Washington, DC: American Psychiatric Publishing; 2012.
50. Rothchild AJ, editor. The evidence-based guide to antipsychotic medications. Washington, DC: American Psychiatric Publishing; 2010.
51. Frankenburg FR, Zanarini MC. Divalproex sodium treatment of women with borderline personality disorder and bipolar II disorder: a double-blind, placebo-controlled pilot study. J Clin Psychiatry. 2002;63:443–6.
52. Hollander E, Allen A, Lopez RP, Bienstock CA, Grossman R, Siever LJ, et al. A preliminary double-blind, placebo-controlled trial of divalproex sodium in borderline personality disorder. J Clin Psychiatry. 2001;62:199–203.
53. Hollander E, Swann AC, Coccaro EF, Jiang P, Smith TB. Impact of trait impulsivity and state aggression on divalproex versus placebo response in borderline personality disorder. Am J Psychiatry. 2005;162:621–4.

54. Loew TH, Nickel MK, Muehlbacher M, Kaplan P, Nickel C, Kettler C, et al. Topiramate treatment for women with borderline personality disorder: a double-blind, placebo-controlled study. J Clin Psychopharmacol. 2006;26:61–6.
55. Nickel MK, Nickel C, Kaplan P, Lahmann C, Muehlbacher M, Tritt K, et al. Treatment of aggression with topiramate in male borderline patients: a double-blind, placebo-controlled study. Biol Psychiatry. 2005;57:495–9.
56. Nickel MK, Nickel C, Mitterlehner FO, Tritt K, Lahmann C, Leiberich PK. Topiramate treatment of aggression in female borderline personality disorder patients: a double-blind, placebo-controlled study. J Clin Psychiatry. 2004;65:1515–9.
57. Tritt K, Nickel C, Lahmann C, Leiberich PK, Rother WK, Loew TH, et al. Lamotrigine treatment of aggression in female borderline-patients: a randomized, double-blind, placebo-controlled study. J Psychopharmacol. 2005;19:287–91.
58. Bogenschutz MP, Nurnberg HG. Olanzapine versus placebo in the treatment of borderline personality disorder. J Clin Psychiatry. 2004;65:104–9.
59. Nickel MK, Muehlbacher M, Nickel C, Kettler C, Gil FP, Bachler E, et al. Aripiprazole in the treatment of patients with borderline personality disorder: a double-blind, placebo-controlled study. Am J Psychiatry. 2006;163:833–8.
60. Pascual JC, Soler J, Puigdemont D, Pérez-Egea R, Tiana T, Alvarez E, et al. Ziprasidone in the treatment of borderline personality disorder: a double-blind, placebo-controlled, randomized study. J Clin Psychiatry. 2008;69:603–8.
61. Schulz SC, Zanarini MC, Bateman A, Bohus M, Detke HC, Trzaskoma Q, et al. Olanzapine for the treatment of borderline personality disorder: a variable-dose, 12-week, randomized, double-blind, placebo-controlled study. Br J Psychiatry. 2008;193:485–92.
62. Soler J, Pascual JC, Campins J, Barrachina J, Puigdemont D, Alvarez E, et al. Double-blind, placebo-controlled study of dialectical behavior therapy plus olanzapine for borderline personality disorder. Am J Psychiatry. 2005;162:1221–4.
63. Simpson EB, Yen S, Costello E, Rosen K, Begin A, Pistorello J, et al. Combined dialectical behavioral therapy and fluoxetine in the treatment of borderline personality disorder. J Clin Psychiatry. 2004;65:379–85.
64. Zanarini MC, Frankenburg FR, Parachini EA. A preliminary, randomized trial of fluoxetine, olanzapine, and the olanzapine-fluoxetine combination in women with borderline personality disorder. J Clin Psychiatry. 2004;65:903–7.
65. Perry JC. Depression in borderline personality disorder: lifetime prevalence at interview and longitudinal course of symptoms. Am J Psychiatry. 1985;142:15–21.
66. Abraham PF, Calabrese JR. Evidenced-based pharmacologic treatment of borderline personality disorder: a shift from SSRIs to anticonvulsants and atypical antipsychotics? J Affect Disord. 2008;111:21–30.
67. Saunders EFH, Silk KR. Personality trait dimensions and the pharmacologic treatment of borderline personality disorder. J Clin Psychopharmacol. 2009;29:461–7.
68. National Institute for Health and Clinical Excellence (NICE). Borderline personality disorder, treatment and management. London: The British Psychological Society and The Royal College of Psychiatrists; 2009. From http://www.nice.org.uk/CG78. Retrieved May 2010.
69. Binks CA, Fenton M, McCarthy L, Lee T, Adams CE, Duggan C. Pharmacological interventions for people with borderline personality disorder. Cochrane Database Syst Rev. 2006;(1): CD005653.
70. Paris J. Treatment of borderline personality disorder. A guide to evidence-based practice. New York: The Guilford Press; 2008.
71. Lieb K, Völlm B, Rücker G, Timmer A, Stoffers JM. Pharmacotherapy for borderline personality disorder: Cochrane systematic review of randomised trials. Br J Psychiatry. 2010;196:4–12.
72. Silk KR, Jibson MD. Personality disorders. In: Rothchild AJ, editor. The evidence-based guide to antidepressant medications. Washington, DC: American Psychiatric Publishing; 2012. p. 139–69.
73. Serban G, Siegel S. Response of borderline and schizotypal patients to small doses of thiothixene and haloperidol. Am J Psychiatry. 1984;141:1455–8.

74. Zanarini MC, Frankenburg FR. Olanzapine treatment of female borderline personality disorder patients: a double-blind, placebo-controlled pilot study. J Clin Psychiatry. 2001;62:849–54.
75. Silk KR, Jibson MD. Personality disorders. In: Rothchild AJ, editor. The evidence-based guide to antipsychotic medications. Washington, DC: American Psychiatric Publishing; 2010. p. 101–24.
76. Silk KR, Feurino III L. Psychopharmacology of personality disorders. In: Widiger TA, editor. The Oxford handbook of personality disorders. New York: Oxford University Press; 2012. p. 713–26.
77. Siever LJ, Davis KL. A psychobiological perspective on the personality disorders. Am J Psychiatry. 1991;148:1647–58.
78. Duggan C, Huband N, Smailagic N, Ferriter M, Adams C. The use of pharmacological treatments for people with personality disorder: a systematic review of randomized controlled trials. Pers Ment Health. 2008;2:119–70.
79. Herpertz SC, Zanarini M, Schulz CS, Siever L, Lieb K, Möller HJ, WFSBP Task Force on Personality Disorders. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of personality disorders. World J Biol Psychiatry. 2007;8:212–44.
80. Ingenhoven T, Lafay P, Rinne T, Passchier J, Duivenvoorden H. Effectiveness of pharmacotherapy for severe personality disorders: meta-analyses of randomized controlled trials. J Clin Psychiatry. 2010;71:14–25.
81. Mercer D, Douglass AB, Links PS. Meta-analyses of mood stabilizers, antidepressants and antipsychotics in the treatment of borderline personality disorder: effectiveness for depression and anger symptoms. J Personal Disord. 2009;23:156–74.
82. Nosè M, Cipriani A, Biancosino B, Grassi L, Barbui C. Efficacy of pharmacotherapy against core traits of borderline personality disorder: meta-analysis of randomized controlled trials. Int Clin Psychopharmacol. 2006;21:345–53.
83. Pramyothin P, Khaodhiar L. Metabolic syndrome with the atypical antipsychotics. Curr Opin Endocrinol Diabetes Obes. 2010;17:460–6.
84. Warnock JK, Morris DW. Adverse cutaneous reactions to mood stabilizers. Am J Clin Dermatol. 2003;4:21–30.
85. Ernst CL, Goldberg JF. The reproductive safety profile of mood stabilizers, atypical antipsychotics, and broad-spectrum psychotropics. J Clin Psychiatry. 2002;63 Suppl 4:42–55.
86. Gentile S. Neurodevelopmental effects of prenatal exposure to psychotropic medications. Depress Anxiety. 2010;27:675–86.
87. Gunderson JG, Morey LC, Stout RL, Skodol AE, Shea MT, McGlashan TH, et al. Major depressive disorder and borderline personality disorder revisited; longitudinal interactions. J Clin Psychiatry. 2004;65:104901056.
88. Zanarini MC, Stanley B, Black DW, Markowitz JC, Goodman M, Pilkonis P, et al. Methodological considerations treatment trials for persons personality disorder. Ann Clin Psychiatry. 2010;22:75–83.
89. Silk KR. The process of managing medications in patients with borderline personality disorder. J Psychiatr Pract. 2011;17:311–9.

Chapter 12
Cognitive Behavioral Therapy-Based Interventions for Borderline Personality Disorder and Mood Disorders

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Introduction

Borderline personality disorder (BPD) is a major public health concern. Existing studies estimate that BPD occurs in 1–3 % of the general population [1–3] and represents 10–20 % of psychiatric outpatient populations and 15–20 % of psychiatric inpatient populations [4, 5]. Despite the serious impact that such a diagnosis has on patients' morbidity and mortality, research has shown that patients can successfully respond to treatment [6, 7]. Though there are several established treatments for BPD including Dialectical Behavioral Therapy (DBT) [8–12], Schema-Focused Therapy (SFT) [13, 14], Transference-Focused Psychotherapy (TFP) [15, 16], and Mentalization-Based Treatment (MBT) [17, 18], these treatments require intensive clinical trainings that are not practical for the nonspecialist practitioner. Moreover, these intensive treatments involve multiple group and individual sessions weekly, along with team or individual supervision. While these therapeutic modalities may be best for patients who can access a specialized personality disorders clinical service, their availability is highly limited in general mental health clinics and individual private practices. Hence, it becomes important to distill out common aspects of these treatments that influence change in patients with BPD and identify broader and more basic approaches that can be practiced widely.

Though each of these empirically validated treatments conceptualizes BPD somewhat differently, all share the goals of increasing self-awareness and self-reflection in addition to decreasing emotional distress. Each modality works to

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address patients' difficulties with self-awareness of their internal experiences and, therefore, difficulties identifying, challenging, and regulating their thoughts and feelings in a meaningful way.

Cognitive Behavioral Therapy (CBT) is a well-established theoretical orientation that specifically highlights the relevance of self-awareness. CBT is based on the premise that patients struggle with structured self-assessment related to maladaptive cognitive processes (i.e., dysfunctional thinking) and behavioral dyscontrol, both of which influence emotional distress. CBT has been widely studied across a number of emotional disorders and has proven effective as both a primary and adjunctive intervention for mood and anxiety disorders. CBT has been modified in order to treat more complex presentations, including BPD [19]. Both DBT and SFT were developed out of recognition that patients with personality disorders and suicidality did not respond to as expected using standard CBT [8, 14]. A significant literature demonstrates the efficacy of the DBT protocol, which involves a skills training group for 120 min once weekly, at least one individual therapy session, on-call skills coaching, and consultation team for the therapist [20–22]. The demand for DBT exceeds the supply of clinicians trained and interested in practicing this modality. As a result, while scientifically proven to be effective, DBT is not generalizable to the clinical practice of most mental health professionals. SFT on the other hand has been found effective in a format involving one to two weekly individual sessions and weekly supervision for the clinician, which makes it a more viable treatment option for the mental health professional working either in a private practice or general clinical setting. However, SFT training and supervision is not widely available.

CBT is a basic psychotherapeutic approach taught most widely in clinical training programs and applicable to the widest range of clinical diagnoses [23]. Its symptom focus and applicability in short courses of treatment allows researchers to easily study its efficacy in a wide range of disorders. These features also enable clinicians trained in CBT to treat a wide variety of patients presenting with complex comorbidities. Studies of CBT in the treatment of BPD show more modest symptomatic improvement compared to the broader range of symptomatic and functional improvements seen in more intensive treatments (e.g., DBT, MBT, SFT, and TFP) [24]. However, on measures of suicidality and depression, both less intensive treatment with CBT and more intensive treatments such as MBT and DBT are effective in treating patients with BPD [25]. While the intensive treatments for BPD may be more broadly efficacious, a less intensive CBT treatment provides a more accessible and practical approach that can and should be widely available to individuals with BPD.

Given CBT's reliance on training patients to (1) increase self-awareness, (2) challenge distorted thoughts, (3) manage impulsive reactions, and (4) regulate emotions, it offers an ideal foundation for treating patients suffering from BPD. CBT therapists first help patients increase their structured self-awareness of their internal states. Secondly, therapists teach patients to integrate cognitive and behavioral skills-based interventions to learn how to regulate their emotions as well as their responses when activated. This chapter will focus on the emergence of

DBT and SFT. Both widely acknowledged therapeutic approaches are outgrowths of CBT designed to more effectively treat patients with characterological problems. A theoretical context is offered to provide a better understanding of how CBT alone can be applied to the treatment of patients with complicated clinical problems, as most therapist do not have access to the specific trainings necessary to implement intensive treatments such as DBT for borderline patients. Neuhaus' Flexible CBT approach is introduced as one possible model that attempts to integrate affective, cognitive, and behavioral interventions by considering specific aspects of the patient while also considering the context of their treatment setting and viability of training the typical practitioner [26].

The Origins of Cognitive Behavioral Therapy

Ellis [27] developed the first CBT treatment, Rational Emotive Therapy (RET), whose basic premise was based on the ancient psychological insight of Epictetus who stated that "what disturbs men's minds is not events but their judgments on events." Ellis proposed that beliefs fuel feelings and hence reactions [27]. He posited that patients get distressed not only because of an event but because of their perspective or belief held as a result of thoughts about the event. This simple model was the first paradigm that distinctly outlined the interplay between events, thoughts, feelings, and subsequent reactions.

A decade later, Aaron Beck further articulated the powerful influence of thought processes on the development and maintenance of mood disorders [28]. He believed that an individual's perception of himself and the world played a key role in his understanding and subsequent reactions to himself and to interpersonal relationships. Beck proposed that people have the potential to generate distorted thoughts when in moments of distress. These distorted thoughts color the intensity of an individual's emotional experience and his subsequent behavioral response. Beck aimed to help patients identify their distorted thoughts in order to evaluate their accuracy as well as their impact on feelings and functioning. Ultimately, Beck hoped that patients would learn a set of skills to identify automatic thoughts, label dysfunctional statements, assess the accuracy of these statements, reevaluate the dysfunctional statements based on "reality," and reframe the statements in ways that better reflect the reality of the situation. Beck, along with other cognitive theorists, believed that through self-awareness and cognitive restructuring, patients had the potential to minimize the development and maintenance of subsequent distress [29].

Beck believed people developed core assumptions throughout their childhood. He believed these assumptions remained unconscious due to the same mechanisms by which other habits of thinking and behaving become integrated and more automatic. His therapeutic approach was therefore focused on training patients to be more aware of their ongoing "stream of consciousness" and to elucidate the expected rigidity around thought patterns. His overarching goal was to teach patients ways of identifying, evaluating, and reframing dysfunctional thought patterns through a collaborative approach between patient and therapist [30].

Jeffrey Young proposed that Beck's model would be particularly challenging to use with patients primarily struggling with Axis II disorders because Beck's model required patients to (1) exhibit readiness to assess their own feelings, (2) identify life problems to work on in treatment, (3) complete homework assignments, (4) develop a solid working alliance with their therapist, and (5) maintain cognitive flexibility in order to make use of the treatment [14]. Young observed that patients with long-standing character problems, such as those with personality disorders, often violate the above expectations. Hence, Young set out to alter Beck's original model to address these limitations and developed a cognitive treatment for patients with complicated clinical presentations.

Schema-Focused Therapy

Young developed a schema-focused model in order to address the limitations inherent in traditional cognitive therapy when treating complex personality disordered patients, such as patients with BPD. SFT is based on the concept that early life experiences of the self in relation to others inform schemas, which then generate dysfunctional patterns of cognition, affect, and behavior. By contextualizing these dysfunctional patterns of cognition, affect, and behavior within a relational context, SFT relates broader personality concerns regarding interpersonal functioning and identity formation to problems of mood, anxiety, and coping. For patients with characterologically unstable relationships and self-concepts, SFT therefore provides a broader basis on which to address more chronic deficits or symptoms related to BPD, not just its acute symptoms of behavioral dyscontrol and affective dysregulation.

SFT importantly relies on the therapeutic relationship as a vehicle of change. In this model, the therapist actively confronts patients about the cognitive and behavioral patterns that have evolved throughout the patient's life. Young describes these patterns as emerging from a lifetime of interactions and experiences between the patient and their context which causes the development of schemas or "organized elements of past reactions and experience that form a relatively cohesive and persistent body of knowledge capable of guiding subsequent perception and appraisals" [31]. Schemas are used as templates, which organize the way individuals make sense of both themselves and their relationships. These orientations may have been helpful at some point in making sense of the world and avoiding distress but gradually develop into ineffective ways of organizing oneself vis a vis reality.

Schemas often inform an individual's thoughts, feelings, behaviors, sense of self, and interpersonal dynamics. According to Young, they develop as a result of ongoing dysfunctional experiences with caregivers, family, or peers during childhood to avoid distress. Schemas are "valid representations" of challenging early experiences and are therefore deeply integrated into one's self perceptions and perceptions of interpersonal relationships. Given the slow emergence of schemas throughout one's life, the template that eventually evolves becomes rigidly entrenched in dysfunctional thought patterns and behaviors. Hence, schemas become very resistant to change. Even when presented with contradictory evidence

that challenges one's schema, the information may be distorted in order to preserve the schema. Young believes that people do this because "the threat of schematic change is too disruptive to the core cognitive organization and hence a variety of cognitive and behavioral maneuvers reinforce the schema" [32]. Schemas get activated throughout life and can generate high levels of emotion that lead to psychological problems such as anxiety, depression, despair, and panic. Ultimately, the activation of schemas may lead to problematic and even self-harming behaviors such as substance use/abuse, self-care problems, or psychosomatic disorders.

Young describes four concepts that perpetuate schemas including (1) schematic maintenance (cognitive and behavioral tendencies that perpetuate the schema), (2) schema avoidance (cognitive, behavioral, and emotional strategies used to avoid the activation of a schema), (3) schema compensation (thoughts or behaviors that overcompensate for the schema and ultimately backfire by promoting schema maintenance), and (4) schema modes (different groupings of schemas that may be activated at the same time). Treatment using this model first involves identifying the patient's schemas, followed by activating the schemas in therapy. Next, the therapist attempts to reconceptualize the schema by providing psychoeducation and proposing a treatment plan which involves the integration of cognitive, behavioral, and interpersonal interventions to assess, challenge, and re-evaluate activated schemas. To a large degree, the focus of schema-focused work involves identifying and then activating the core schema using a range of cognitive and behavioral techniques in the context of the patient-therapist relationship [33]. Techniques for SFT relevant to the change phase of treatment are outlined in Table 12.1.

Table 12.1 Schema-focused therapy change phase strategies [14]

Cognitive strategies
Testing schema validity
Reframing supportive evidence for schemas
Evaluating advantages and disadvantages of current coping style
Dialogues between "healthy" and "schema" sides
Schema flash cards
Schema diary forms
Experiential strategies
Guided imagery
Letters to parents
Behavioral pattern-breaking strategies
Flash cards
Imagery
Dialogues
Relaxation training
Assertiveness training
Anger management
Self-control strategies (i.e., self-monitoring, goal-setting, self-reinforcement)
Graduated exposure to feared situation

Data Source: Young et al. [14]

Schema-focused treatment offers an enhanced model for understanding complicated psychopathology based on the integration of traditional cognitive behavioral techniques and special attention to interpersonally based schemas that prompt dysfunctional behavior, cognition, and affect in the context of relational triggers. SFT's attention to the patient's interpersonal sensitivities, conceptualization of relationships, and relational functioning overlaps with the core focus of both MBT and TFP. In all three treatments, the interactions between the therapist and patient are considered relevant representations of symptomatic patterns and are actively analyzed and reorganized in session. Spinhoven and colleagues [34] proposed that both the therapeutic alliance as well as specific schema-focused treatment techniques interact to influence patients' success in SFT [34]. However, the exact process through which patients generalize and make changes has yet to be established. More research is required to fully understand the effectiveness of SFT as well as the process through which patients with BPD change using this therapeutic approach.

The Emergence of DBT from CBT

Marsha Linehan appreciated the powerful effect of CBT's theory and specifically recognized the relevance of this theoretical approach to patients with complicated clinical profiles. Linehan found that the efficacy of a basic CBT orientation in treating patients with self-harming and suicidal tendencies was limited. She modified standard CBT to suit these recurrently suicidal patients, who beyond their acute self-destructive tendencies had BPD. In her treatment, which she later called Dialetical Behavioral Therapy (DBT), she organized the basic premise of a CBT treatment around the problem of emotional dysregulation, which she posited to be the core feature of BPD. In addressing this core feature of the borderline individual's emotional dysregulation, Linehan integrated both mindful and validating techniques. While mindfulness worked to increase the individual's tolerance and effective management of emotions, validation served to mitigate the tendency for symptomatic reactions to responses from others.

Linehan's explanation of the biosocial theory of BPD implicates both biological and environmental factors in the development of the disorder. She proposed that there is a transactional relationship between genes and environment that leads to difficulties in learning, labeling, expressing, and modulating emotions. Linehan explains BPD's core vulnerability as an outcome of the interface between an individual's emotional sensitivity and their environment's ineffective and invalidating responses towards the individual's expressions of their emotional vulnerabilities. In an invalidating environment, caregivers punish, correct, trivialize, or ignore the child's expressions of private experiences. Over time, individuals in these environments learn to doubt their ability to interpret their internal experiences or self-invalidate and instead look to the environment to help label, organize, and express emotions. As a result, a person with BPD has little self-awareness of their internal

states or the ways in which their emotions are connected to thoughts and behaviors. These individuals often oscillate between extreme emotional expression and complete emotional inhibition. In DBT, patients learn to regulate their emotions by increasing their skills to both self-assess and self-regulate.

In developing this model, Linehan outlined very clear instructions as to how a patient can self-assess and reevaluate one's thoughts, feelings, and subsequent reactions when distressed. DBT focuses on four modules including distress tolerance, emotion regulation, interpersonal effectiveness, and mindfulness. Each module clearly outlines specific skills patients can use to self-assess and self-regulate in order to decrease impulsive and self-harming behaviors. Linehan's model also includes psychoeducation about how patients could better understand and later intervene across these four domains [9].

Core mindfulness skills, a key component of DBT, train individuals to increase self-awareness by being present in the moment. Mindfulness is defined as "paying attention in a particular way: on purpose, in the present moment, and nonjudgmentally" [35]. Mindfulness involves refocusing attention away from distressing and distracting thoughts, feelings, and behaviors and instead attending to and participating in the current context. Training individuals to fully engage in the present moment is challenging; therefore, DBT outlines specific skills to facilitate the development of a mindful stance. Linehan enumerates three guidelines, called the "what" skills, to clarify steps involved in practicing mindfulness: *observe* (actively observing whatever is happening in oneself and one's environment), *describe* (applying verbal labels to the situation, being as objective as possible in order to more accurately outline the events), and *participate* (entering completely into the present activity without self-consciousness, fully engaging with both mind and body). Individuals are further instructed by the three "how" skills, which ask them to engage in mindful activities *nonjudgmentally*, *one-mindfully* (doing one thing at a time), and *effectively* (doing what works).

By following the "what" and "how" skills of mindfulness, individuals with BPD can increase their capacity for emotional and behavioral control. Developing a mindful stance in the face of emotional stimulation allows individuals with BPD to more effectively identify, label, evaluate, and manage their responses to otherwise tumultuous situations [36]. Increasing control involves cultivating an acute awareness of one's own unique thoughts and behaviors and how they impact emotional experiences, as well as implementing more effective ways of responding to these internal states. Through full participation using a mindful stance, individuals with BPD can develop the capacity to label their private experiences more accurately and evaluate these experiences using structured techniques. This increased structured self-awareness leads to more effective processing of emotional experiences and facilitates the integration of effective behavioral responses into an individual's coping style.

The organization of DBT's content and techniques around a core formulation of BPD in Linehan's biosocial theory enhances its coherence as a relevant treatment approach for both clinicians and patients. The use of validation as a balancing point to imperatives to change is thought to make DBT more tolerable to patients with

BPD who are prototypically rejection and criticism sensitive. According to biosocial theory, patients with BPD will become *more* not *less* emotionally dysregulated if confronted with their problems without simultaneous acknowledgment from the therapist of the reasons why the patient developed those symptomatic adaptations. DBT's incorporation of mindfulness techniques as a core skill set may also ameliorate other symptoms often found to be comorbid with BPD, ranging from mood [37, 38], anxiety [39, 40], eating [41, 42], and substance use disorders [43]).

However, as previously argued, DBT and SFT adaptations of CBT for BPD populations require intensive training for therapists and may not be available to the majority of patients suffering from BPD. Understanding the effective adaptations of CBT in DBT and SFT can inform more accessible and effective approaches to managing complex clinical profiles. All of the existing manualized evidence-based approaches to BPD integrate a basic understanding of the core problems underlying the complex symptom profile of these patients. While the formulation of the core problem of BPD differs among the approaches, each educates the practitioner to understand BPD as a syndrome and to organize technique around these formulations. Structured clinical or general management approaches, which are based primarily on an informed understanding of BPD, have more recently been found to be effective for reducing symptoms of the disorder with less intensive treatment [44, 45]. In addition, both DBT and SFT emphasize management of the therapeutic relationship between the therapist and the patient with BPD, who presents with both limitations in reflective capacities as well as inherent interpersonal sensitivities. We consider these three features—a basic formulation of the problems of BPD, interpersonal management of the therapeutic relationship according to an understanding of BPD, and an expectation of limitations in self-awareness and reflectiveness as a core problem of BPD—as essential to the adaptation of any therapeutic approach to treating BPD patients.

CBT as a Relevant Framework

Given the complex issues that arise when treating patients with characterological problems in "real-world" clinical contexts, it becomes important to identify a theoretical framework that has validity in treating patients with a range of problems. CBT, as described earlier, is a clearly outlined, well-established treatment approach that has received growing attention due to its efficacy and effectiveness in treating patients with a host of disorders [46]. Though there is some controversy in the field of psychotherapy research about what factors predict change in treatment, the growing consensus is that CBT is a well-supported orientation for treating mood, anxiety, and some personality disorders [47]. Despite the ongoing debate about whether "specific factors" or "common factors" (i.e., therapeutic alliance, expectancy factors, and hope) account for change in therapy, there is clear evidence that cognitive and behavioral therapies can be implemented

effectively in a variety of contexts and diagnoses, which makes it appealing for real-world clinical situations [48].

Some mental health researchers have proposed that cognitive and behavioral therapies are consistently effective in treating patients with emotional disorders because such orientations focus on helping patients confront their problems, including confronting their fears [49]. According to Weinberger [49], helping patients confront their fears is a critical aspect of successful therapies, and he views this as a common factor across several theoretical orientations. Weinberger [49] proposes that perhaps CBT is more effective in the treatment of particular disorders because exposure (i.e., confronting fears) is a central focus of most CBT treatments [49].

While CBT may not be the gold standard for treatment of BPD, it is a widely available treatment regarded as effective in the treatment of disorders which commonly co-occur with BPD, especially mood disorder [37–43]. Studies suggest that CBT is as effective as antidepressant medication and other forms of psychotherapy in reducing symptoms of depression and maintaining remission [50]. It is also found to be effective in conjunction with medication management in the prevention of relapse in bipolar disorder, reduction in length of mood episodes and medication use, as well as increase in coping with bipolar symptoms and social functioning [51, 52]. Though pharmacotherapy has been the predominant treatment approach for patients with mood disorders, medication alone fails to prevent recurrence in patients approximately 50–75 % over several years [53, 54]. Even when patients are responsive to pharmacotherapy, there are additional problems associated with using medications as the only intervention to manage the illness. Patients who are responsive to pharmacotherapy often struggle with basic aspects of adherence to a medication regimen thereby increasing relapse in bipolar symptoms. Approximately 50 % of patients who manage their illness via pharmacotherapy have at least one episode of noncompliance with their medication regimen [55]. For many patients, particular medications may be contraindicated due to psychiatric or medical comorbidities or intolerance of side effects, so psychotherapy may be indicated as the treatment with the best risk-benefit profile. In addition, many patients prefer psychological treatments over psychopharmacologic treatments [56].

As noted throughout this book, depression and BPD are estimated to co-occur in up to 70 % cases of BPD [57] and can co-occur with or be misdiagnosed as bipolar disorder. The evidence that CBT is effective for this group of disorders suggests that CBT is a practical treatment approach for patients with BPD and a mood disorder when specialized intensive treatments such as DBT, SFT, MBT, or TFP are unavailable. More research is needed to confirm the effectiveness of CBT approaches in patients with comorbid mood and borderline personality disorder, but until such research is available, understanding the common features of CBT approaches to mood disorders and modified CBT protocols for BPD, such as DBT, may help the general clinician tailor their psychotherapeutic treatment plan for the complex patient with these comorbidities.

Table 12.2 Corresponding overlaps IPSRT and DBT

IPSRT	DBT
Identify connections between mood changes and life events	Identify connections between life events, thoughts, emotions, impulses, and behaviors
	With attention to possible skills-based interventions and consideration of natural consequences of behavior (*chain analysis*, *emotion regulation*)
Maintain predictable and stable daily rhythms such as wake/sleep patterns	Maintain self-care routines to minimize emotional vulnerability
	Emphasis on sleep, *exercise*, *physical health*, *elimination of substance misuse*, *and building of mastery* (*emotion regulation module*)
Identify and ultimately manage triggers towards increased emotional dsyregulation with a particular focus on interpersonal triggers	Improve interpersonal effectiveness (*interpersonal effectiveness module*)
	Manage distress from stressful events to accept reality and survive crisis without making a situation worse (*distress tolerance*)
Mourn the loss of a healthy self	Acceptance of once own vulnerabilities and reality as it is (*radical acceptance/distress tolerance*)
Identify and manage emotional symptoms	Increase self-awareness and non-reactivity to internal states (*mindfulness*)

Several specific treatment approaches have been examined to assess the efficacy of psychotherapy in conjunction with medication management to optimize patient functioning and minimize recurrence in patients with bipolar disorder. Frank and colleagues [58] compared two established psychosocial interventions for treating bipolar patients including interpersonal and social rhythm therapy (IPSRT) and a therapy that focused on intensive clinical management [58]. IPSRT is a manualized evidence-based treatment approach developed as an adaptation of CBT for bipolar disorder.

ISPRT was developed based on acknowledgment that both biological factors as well as psychosocial factors play integral roles in determining the course and outcome in treating patients with bipolar disorder [59]. The overlaps between core features of IPSRT and DBT are also illustrated in Table 12.2. Both approaches integrate basic cognitive behavioral techniques to stabilize the affective instability observed in both BPD and bipolar disorder. DBT as well as other mindfulness-based approaches have proven effective for patients with bipolar disorder [37, 38]. There are shared features which target underlying emotional factors and vulnerabilities shared between these disorders.

Lauder and colleagues proposed that the success of these psychotherapeutic approaches may be related to elements that are shared across these psychotherapeutic treatments [60]. They suggested that these varied treatment approaches similarly rely on psychoeducation of the illness, teaching patients specific skills to manage their illness, increased adherence to the treatment approach, increased awareness of the factors that influence the onset and maintenance of an episode/relapse,

implementation of relapse prevention strategies, and an overall focus on the relevance of interpersonal dynamics to the stabilization of symptoms. The basic CBT model appears to provide a foundation for treating even disorders thought to be heavily biologically based. Psychotherapeutic approaches appear to be valuable in the treatment of bipolar illness though future research should focus on which interventions are most helpful for particular patients.

The idea that psychotherapeutic approaches can be individualized for patients is not a new concept. In fact, there is an age-old debate about what psychotherapies work for whom [61]. This debate highlights how relevant it is that practitioners identify not only theoretical orientations that are effective in treating patients but also outline the specific factors that influence change. Consideration of the unique presentation of the patient in the context of the therapeutic alliance is paramount in the process of utilizing an evidence-based approach effectively. Persons has long emphasized the importance of examining clinicians' adaptations of evidence-based research protocols. Her work focuses primarily on CBT-oriented interventions and the clinician's corresponding assessment of the individual patient in order to better understand how patients change in therapy [62]. Persons's [62] case formulation approach has been a foundation for clinicians applying CBT in the uncontrolled conditions of clinics and private practices [63]. It is with this orientation in mind that we present Neuhaus' Flexible CBT model of treatment.

The Flexible CBT Approach

Neuhaus described the relevance of examining the ways in which CBT can be systematically applied to a range of emotional disorders in "real-world" clinical contexts and also described the ways in which patients can generalize change. Neuhaus was specifically interested in examining the ways in which the theoretical underpinnings of CBT could be flexibly applied to complex clinical profiles such as patients presenting with comorbid mood disorders and characterological problems. He used Persons's [62] case formulation approach as the foundation for examining the translation of findings from controlled clinical trials to real-world clinical contexts where conditions for treatment are, by definition, uncontrolled [64].

Neuhaus' flexible CBT approach systemically distills common interventions, which he calls components, across CBT protocols and matches those CBT interventions to the most prominent symptoms and functional problems of patients who typically present with comorbid and complicated clinical diagnoses. In effect, the logic is consistent with the unified treatment introduced by Persons [62] as symptoms and functional problems take priority over one specific diagnosis. Neuhaus further described the translation of CBT interventions to generalized change in a patient's life. Neuhaus was concerned with identifying the ways in which patients with complicated clinical profiles made changes both in sessions and then generalize these changes to all areas of life using a CBT framework [64]. He outlined

Doss's model of change for psychotherapy as a useful model for conceptualizing skill acquisition in CBT [65].

Doss's model outlines three components of change: change processes, change mechanisms, and therapy outcome. Change processes reflect what occurs in the actual therapy session or through directed homework. Change processes are broken down into two components: what the therapist does regarding directed interventions (e.g., following a protocol) and what the patient does as a direct result of therapist interventions in the session or through homework assignments. Change processes are assumed to lead to improvements in patient characteristics or skill use outside of the therapy session. These patient changes outside the session are change mechanisms that are an intermediate stage of change on the way to the desired therapy outcome (e.g., symptom reduction, improvements in functioning). The full sequence of this model of change is as follows: the therapist directs interventions in the therapy sessions and patient responds (change processes), which leads to the patient making positive changes in using skills in everyday life (change mechanisms) and ultimately to the desired therapy outcome (fewer symptoms and better functioning) [65]. It is important to note that change mechanisms are not under direct control of the therapist because they occur outside of the session.

While analogous to the unified approach for emotional disorders developed in a more research-based context, Neuhaus' flexible approach was developed in the context of naturalistic treatment settings (i.e., partial hospital, intensive outpatient, and outpatient levels of care) to respond to patients with complicated psychiatric profiles. His overarching goal was to provide a treatment model that could be accessible to the general practitioner. He proposed using a CBT model given its efficacy across different clinical problems and hoped to train practitioners to apply CBT skills-based interventions based on the symptomatology and functional deficit presented by the patient. Neuhaus' model has since been examined in such "real-world" clinical contexts and has been shown to be effective in treating these complicated presentations patients [63].

Neuhaus outlined basic aspects of CBT that appeared common across established interventions and proposed to match these interventions to functional problems. According to Neuhaus, the flexible CBT approach involves the following common interventions: (1) cognitive components to identify maladaptive life patterns and change negative thought processes associated with mood and anxiety symptoms; (2) behavioral components for behavioral activation and activity planning to address low motivation, experiential avoidance, lack of daily structure, and social isolation; and (3) both cognitive and behavioral components for preventing relapse [64]. Psychoeducation plays a substantial role, particularly in the early stages of treatment.

In short, the flexible CBT approach guides clinical decision-making in real-world clinical contexts to match the skills-based intervention to the individual and complex patient. The therapist uses a set of empirically supported, skills-based interventions (e.g., guided discovery, thought records, behavioral activation), but the timing, sequence, and emphasis will vary according to patient needs. Diagnosis, comorbidities, personality factors, and the therapeutic relationship all contribute to the formulation that guides the therapist in how to match treatment interventions (e.g., skills) to patients [64].

Conclusions

Given the relatively high prevalence rate of BPD in the general population coupled with the challenges associated with engaging these patients in treatment, identifying effective interventions that are accessible to the general practitioner to treat patients with BPD becomes necessary. CBT is a well-established treatment that has been shown to be effective across a host of clinical disorders and is the basis for DBT and SFT, two intensive specialized evidence-based treatments for BPD. A flexible CBT approach was offered to address the need to treat complicated cases by distilling and matching cognitive and behavioral interventions to the most prominent symptoms and functional problems of patients with complicated clinical profiles. The flexible CBT approach highlights the need to develop a comprehensive and skills-based treatment that can be applied by the general practitioner to patients with complicated clinical presentations, such as patients suffering from BPD. More research needs to be done to identify how less intensive and more widely available therapeutic approaches implemented by generalist mental health practitioners can utilize common effective ingredients using CBT for patients who have both mood disorders and BPD or a differential diagnosis including both BPD and bipolar disorder.

References

1. Zimmerman M, Coryell W. The reliability of personality disorder diagnoses in a nonpatient sample. J Pers Disord. 1989;3:53–7.
2. Swartz M, Blazer D, George L, Winfield I. Estimating the prevalence of borderline personality disorder in the community. J Pers Disord. 1990;4(3):257–72.
3. Torgersen S, Kringlen S, Cramer V. The prevalence of personality disorder in a community sample. Arch Gen Psychiatry. 2001;58:590–6.
4. Kass F, Skodol A, Charles E, Spitzer R, Williams J. Scaled ratings of DSM-III personality disorders. Am J Psychiatry. 1985;142:627–30.
5. Gunderson JG. Borderline personality disorder: a clinical guide. Washington, DC: American Psychiatric Publishing; 2001.
6. Zanarini MC, Frankenburg FR, Reich DB, Fitzmaurice G. Attainment and stability of sustained symptomatic remission and recovery among patients with borderline personality disorder and axis II comparison subjects: a 16-year prospective follow-up study. Am J Psychiatry. 2012;169:476–83.
7. Gunderson JG, Stout RL, McGlashan TH, Shea MT, Morey LC, Grilo CM, et al. Ten-year course of borderline personality disorder: psychopathology and function from the Collaborative Longitudinal Personality Disorders Study. Arch Gen Psychiatry. 2011;68:827–37.
8. Linehan MM. Cognitive behavioral treatment of borderline personality disorder. New York: Guilford; 1993.
9. Linehan MM. Skills training manual for treating borderline personality disorder. New York: Guildford; 1993.
10. Koons CR, Robins CJ, Bishop GK, et al. Efficacy of dialectical behavioral therapy in women veterans with borderline personality disorder: a randomized controlled trial. Behav Ther. 2001;32:371–90.
11. Verheul R, Van Den Bosch LM, Koeter MW, et al. Dialectical behavior therapy for women with borderline personality disorder: 12-month, randomized clinical trial in the Netherlands. Br J Psychiatry. 2003;182:135–40.

12. Bohus M, Haaf B, Simms T, Limberger MF, Schmahl C, Unckel C, et al. Effectiveness of inpatient dialectical behavioral therapy for borderline personality disorder: a controlled trial. Behav Res Ther. 2004;42:487–99.
13. Giesen-Bloo J, van Dyck R, Spinhoven P, van Tilburg W, Dirksen C, van Asselt T, et al. Outpatient psychotherapy for borderline personality disorder: randomized trial of schema-focused therapy vs transference-focused psychotherapy. Arch Gen Psychiatry. 2006;63(6): 649–58.
14. Young JE, Klosko JS, Weishaar ME. Schema therapy: a practitioner's guide. New York: The Guilford Press; 2003.
15. Clarkin JF, Levy KN, Lenzenweger MF, Kernberg OF. Evaluating three treatments for borderline personality disorder: a multiwave study. Am J Psychiatry. 2007;164(6):922–8.
16. Clarkin JF, Yeomans F, Kerberg OF. Psychotherapy of borderline personality: focusing on object relations. Washington, DC: American Psychiatric Publishing, Inc; 2006.
17. Bateman A, Fonagy P. Effectiveness of partial hospitalization in the treatment of borderline personality disorder: a randomized controlled trial. Am J Psychiatry. 1999;156:1563–9.
18. Bateman A, Fonagy P. Treatment of borderline personality disorder with psychoanalytically oriented partial hospitalization: an eighteen month follow-up. Am J Psychiatry. 2001;158: 36–42.
19. Chambless DL, Ollendick TH. Empirically supported psychological interventions: controversies and evidence. Annu Rev Psychol. 2001;52:685–716.
20. Linehan MM, Comtois KA, Murray AM, Brown MZ, Gallop RJ, Heard HL, et al. Two-year randomized controlled trial and follow-up of dialectical behavior therapy vs therapy by experts for suicidal behaviors and borderline personality disorder. Arch Gen Psychiatry. 2006; 63(7):757–66.
21. Harned MS, Chapman AL, Dexter-Mazza ET, Murray A, Comtois KA, Linehan MM. Treating co-occurring Axis I disorders in recurrently suicidal women with borderline personality disorder: a 2-year randomized trial of dialectical behavior therapy versus community treatment by experts. J Counsult Clin Psychol. 2008;76(6):1068–75.
22. McMain SF, Guimond T, Streiner DL, Cardish RJ, Links PS. Dialectical behavior therapy compared with general psychiatric management for borderline personality disorder: clinical outcomes and functioning over a 2-year follow-up. Am J Psychiatry. 2012;169(6):650–61.
23. Beck JS. Cognitive behavioral therapy: basics and beyond. 2nd ed. New York: Guilford Press; 2011.
24. Davidson K, Norrie J, Tyrer P, Gumley A, Tata P, Murray H, et al. The effectiveness of cognitive behavior therapy for borderline personality disorder: results from the borderline personality disorder study of cognitive therapy (BOSCOT) trial. J Pers Disord. 2006;20(5):450–65.
25. Davidson KM, Tran CF. Impact of treatment intensity on suicidal behavior and depression in borderline personality disorder: a critical review. J Pers Disord. 2014;28(2):181–97.
26. Neuhaus EC. Fixed values and a flexible partial hospital program model. Harv Rev Psychiatry. 2006;14:1–14.
27. Ellis A. Rational psychotherapy. J Gen Psychol. 1958;59:35–49. Reprinted: New York: Institute for Rational-Emotive Therapy.
28. Beck AT. Cognitive therapy and the emotional disorders. New York: International Universities Press; 1976.
29. Beck AT, Rush AJ, Shaw BF, Emery G. Cognitive therapy for depression. New York: Guilford Press; 1979.
30. Beck AT, Steer RA, Brown GK. Manual for the beck depression inventory-II. San Antonio: Psychological Corporation; 1996.
31. Segal ZV. Appraisal of the self-schema construct in cognitive models of depression. Psychol Bull. 1988;103:147–62.
32. McGinn LK, Young JE. Schema-focused therapy. In: Salkovskis PM, editor. Frontiers of cognitive therapy. New York: Guilford Press; 1996. p. 182–207.
33. Young J, Klosko J. Schema therapy. In: Oldham JM, Skodol AE, Bender DS, editors. The American Psychiatric Publishing textbook of personality disorders. 1st ed. Arlington: American Psychiatric Publishing; 2005. p. 289–306.

34. Spinhoven P, Bockting CL, Kremers IP, Schene AH, Mark J, Williams G. The endorsement of dysfunctional attitudes is associated with an impaired retrieval of specific autobiographical memories to matching cues. Memory. 2007;15:324–38.
35. Kabat-Zinn J. Wherever you go, there you are: mindfulness meditation in everyday life. New York: Hyperion; 1994.
36. Lynch TR, Chapman AL, Rosenthal MZ, Kuo JR, Linehan MM. Mechanisms of change in dialectical behavior therapy: theoretical and empirical observations. J Clin Psychiatry. 2006;62:459–80.
37. Van Dijk S, Jeffrey J, Katz MR. A randomized, controlled, pilot study of dialectical behavior therapy skills in a psychoeducational group for individuals with bipolar disorder. J Affect Disord. 2013;145(3):386–93.
38. Deckersbach T, Hölzel BK, Eisner LR, Stange JP, Peckham AD, Dougherty DD, et al. Mindfulness-based cognitive therapy for nonremitted patients with bipolar disorder. CNS Neurosci Ther. 2012;18(2):133–41.
39. Vollestad J, Nielsen MB, Nielsen GH. Mindfulness- and acceptance-based interventions for anxiety disorders: a systematic review and meta-analysis. Br J Clin Psychol. 2012;51(3): 239–60.
40. Hofe EA, Bui E, Marques L, Morris LK, Robinaugh DJ, Worthington JJ, et al. Randomized controlled trial of mindfulness meditation for generalized anxiety disorder: effects of anxiety and stress reactivity. J Clin Psychiatry. 2013;74(8):786–92.
41. Kristeller JL, Baer RA, Quillian-Wolever R. Mindfulness-based approaches to eating disorders. In: Baer RA, editor. Mindfulness-based treatment approaches: clinician's guide to evidence base and applications. Amsterdam/Boston: Elsevier, Academic Press; 2006.
42. Wanden-Berghe RG, Sanz-Valero J, Wanden-Berghe C. The application of mindfulness to eating disorders treatment: a systematic review. Eat Disord. 2011;19(1):34–48.
43. Chiesa A, Serretti A. Are Mindfulness-Based Interventions Effective for Substance Use Disorders? A Systematic Review of the Evidence. Subst Use Misuse. 2014;49(5):492–512.
44. McMain SF, Links PS, Gnam WH, Guimond T, Cardish RJ, Korman L, et al. A randomized trial of dialectical behavior therapy versus general psychiatric management for borderline personality disorder. Am J Psychiatry. 2009;166(12):1365–74.
45. Bateman A, Fonagy P. Randomized controlled trial of outpatient mentalization-based treatment versus structured clinical management for borderline personality disorder. Am J Psychiatry. 2009;166(12):1355–64.
46. Chambless DL. Beware the dodo bird: the dangers of overgeneralization. Clin Psychol Sci Pract. 2002;9(1):13–6.
47. Task Force on Promotion and Dissemination of Psychological Procedures. Division of Clinical Psychology, American Psychological Association. Training in and dissemination of empirically validated psychological treatments: reports and recommendations. Clin Psychol. 1995;48:3–23.
48. Chambless DL. Identification of empirically supported psychological interventions. Clin Res Dig Suppl Bull. 1996;14(6):1–2.
49. Weinberger J. Common factors aren't so common: the common factor dilemma. Clin Psychol Sci Pract. 1995;2(1):45–69.
50. Driessen ED, Hollon SD. Cognitive behavioral therapy for mood disorders: efficacy, moderators and mediators. Psychiatr Clin North Am. 2010;33(3):537–55.
51. Lam DH, Watkins ER, Hayward P, et al. A randomized controlled study of cognitive therapy for relapse prevention for bipolar affective disorder. Arch Gen Psychiatry. 2005;162(2):145–52.
52. Lam DH, Hayward P, Watkins ER, et al. Relapse prevention in patients with bipolar disorder: cognitive therapy outcome after 2 years. Am J Psychiatry. 2006;67(2):324–29.
53. Hollon SD, Thase ME, Markowitz JC. Treatment and prevention of depression. Psychol Sci Public Interest. 2002;3.
54. Markar HR, Mander AJ. Efficacy of lithium prophylaxis in clinical practice. Br J Psychiatry. 1989;155:496–500.
55. Zaretsky AE, Sakina R, Sagar VP. How well do psychosocial interventions work in biopolar disorder? Can J Psychiatry. 2007;52:14–21.

56. McHugh RK, Whitton SW, Peckham AD, Welge JA, Otto MW. Patient preference for psychological vs pharmacologic treatment of psychiatric disorders: a meta-analytic review. J Clin Psychiatry. 2013;74(6):595–602.
57. Skodol AE, Stout RL, McGlashan TH, Grilo CM, Gunderson JG, Shea MT, et al. Co-occurrence of mood and personality disorders: a report from the collaborative longitudinal personality disorders study (CLPS). Depress Anxiety. 1999;10(4):175–82.
58. Frank E, Kupfer DJ, Thase ME, Mallinger AG, Swartz HA, Fagiolini AM, et al. Two-year outcomes for interpersonal and social rhythm therapy in individuals with bipolar I disorder. Arch Gen Psychiatry. 2005;62(9):996–1004.
59. Goodwin FK, Jamison K. Manic-depressive illness: bipolar disorders and recurrent depression. 2nd ed. New York: Oxford University Press; 2007.
60. Lauder SD, Berk M, Castle DJ, Dodd S, Berk L. The role of psychotherapy in bipolar disorder. Med J Aust. 2010;193(4):S31–5.
61. Hubble MA, Duncan BL, Miller SD. Introduction. In: Hubble MA, Duncan BL, Miller SD, editors. The heart and soul of change: what works in therapy. Washington, DC: American Psychological Association; 1999. p. 1–19.
62. Persons JB. The case formulation approach to cognitive-behavioral therapy. New York: The Guilford Press; 2008.
63. Christopher MS, Jacob KL, Neuhaus EC, Neary TJ, Fiola LA. Cognitive and behavioral changes related to symptom improvement among patients with a mood disorder receiving intensive cognitive-behavioral therapy. J Psychiatr Pract. 2009;15(2):95–102.
64. Neuhaus EC. The flexible CBT approach. (Online Textbook). Lincoln: TRi Behavioral, LLC; 2008. www.tribehavioral.com.
65. Doss BD. Changing the way we study change in psychotherapy. Clin Psychol Sci Pract. 2004;11:368–86.

Chapter 13
Psychodynamic Treatment for Borderline Personality Disorder and Mood Disorders: A Mentalizing Perspective

Patrick Luyten and Peter Fonagy

Introduction

Considering the comorbidity between depression and BPD is important from both a research and a clinical perspective. Studies not only suggest that depression and BPD are highly comorbid, but also that comorbidity with BPD features may influence the clinical course as well as treatment response in depression in negative ways [1, 2]. Similarly, depression or dysphoria is a core feature of BPD, although studies suggest that depression in BPD has a different character than in MDD [3, 4]. As we will argue in this chapter, differences in the phenomenology of depression in BPD have often been neglected, despite the fact that they have very important implications for treatment and point to substantial differences in the development and course of these disorders.

From a mentalizing perspective, we believe that (brief) focused treatments that are effective in more high-functioning patients suffering from depression are likely to be less effective with depressed patients with (marked) BPD features if the treatment model is not adapted to the specific characteristics of these patients. Patients with BPD suffer from marked impairments in their mentalizing capacities—that is, in their capacity to understand the self and others in terms of intentional mental states, such as feelings, desires, wishes, values, and goals. Particularly in severely

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disturbed BPD patients, treatments that strongly rely on reflective capacities might actually become iatrogenic [5, 6]. We argue that the reasons for this lie in differences in the attachment history and impairments in mentalizing, and related epistemic hypervigilance [7], in patients with (severe) BPD features versus those without. These differences are presumed to have a negative impact on the treatment of these patients, as they (a) impede the development of a therapeutic alliance, a key predictor of therapeutic outcome in evidence-based treatments for depression, regardless of the type of treatment [8], and (b) are negatively related to the patient's ability to benefit from both brief and longer-term supportive and particularly expressive (i.e., insight-oriented) treatments [9]. Although it is not yet clear whether depression and BPD are part of a spectrum of affective disorders, we consider it helpful from a treatment perspective to think of depressed patients as situated on a continuum ranging from depressed patients without BPD features to depressed patients with marked BPD features, necessitating a different treatment approach depending on their position on this continuum. Briefly, depressed patients without marked BPD features may benefit from a *mental representations* approach [10], that is, an approach that focuses on distortions in the content and/or developmental level of mental representations (cognitive–affective schemas or internal working models of self and others). Yet, the more patients move to the borderline end of the spectrum, the less likely they become to benefit from this approach, to the point that such an approach may become iatrogenic. Such patients may benefit more from a *mental process* or *mentalizing* approach, where the focus is on distortions in processes related to the metacognitive ability to reflect on the self and others [10, 11].

In this chapter, we first review, with an attachment/mentalizing focus in mind, relevant empirical research concerning comorbidity between BPD and depression and similarities and differences in the etiology of these disorders. Next, we describe a mentalization-based spectrum of interventions for depressed patients with varying levels of BPD comorbidity, with different weight given to mental representation and mental process models depending on the severity of BPD comorbidity. We also provide preliminary evidence supporting the effectiveness of mentalization-based treatments in depression.

Comorbidity Between BPD and Mood Disorders

Depression is a highly prevalent disorder, with population-based studies suggesting a lifetime prevalence for unipolar depression of 15 % and up to 25 % in women [12–14]. Depression is expected to be the second most serious disorder with respect to the global disease burden by the year 2020 [15]. Studies suggest that unipolar depression has a relapse rate of 20–30 % within 3 years following a first episode and 70–80 % within 3 years in subjects who have had three or more depressive episodes [16]. The probability of at least one further episode of depression after a first episode is estimated to be almost 90 % [17], and the average depressed patient will experience four episodes during their lifetime, each approximately 20 weeks in duration [18]. A notable illustration of the long-term negative impact of mood

disorders is given by the finding that children of parents with mood disorders are themselves at higher risk of developing psychopathology in later life [19]; both internalizing and externalizing disorders are more common in the children of parents with mood disorders [20].

Studies have shown that currently used pharmaceutical and psychotherapeutic treatments have limited efficacy for a considerable proportion of depressed individuals, with only around 50 % of depressed patients responding to these treatments [21–23]. As a consequence, treatment guidelines have emphasized the need for a long-term approach in depression management, stressing continuation and treatment maintenance, and with a focus on relapse prevention [21].

One reason for the relatively limited response of many depressed patients in current evidence-based treatments [e.g., 24] may lie in the high comorbidity between MDD and BPD [22, 25–27]. Lower response rates in depressed patients with BPD have often been reported [28, 29]. For instance, in a large study of 276 patients with MDD, randomized to interpersonal psychotherapy or pharmacotherapy, higher levels of personality pathology and the presence of BPD in particular were associated with a longer time to remission [2]. However, some higher quality studies tend not to show an influence of BPD comorbidity [30]. This may be the case for at least two reasons. First, patients with marked BPD features (e.g., high levels of parasuicidal behavior and impulsivity) might simply be excluded, particularly in high-quality studies. Westen and colleagues, for instance, found a high correlation between the number of exclusion criteria (as an indicator of the quality of the study) and treatment outcome in studies of depression and anxiety [31]. Second, therapists who are closely supervised and monitored, as is typically the case in high-quality studies, might be more likely to tailor their treatment and interventions. Hilsenroth and colleagues, for instance, showed that short-term psychodynamic psychotherapy was equally effective for depressed patients with and without comorbid borderline pathology. Yet in patients with comorbid BPD features, therapists used more structuring techniques than in patients without comorbid borderline pathology. These included providing structure at the start of therapy, suggesting specific activities between sessions, maintaining an active focus on treatment topics, more supportive interventions, and more interventions aimed at examining relational patterns [29]. These adaptations in techniques are, in our opinion, not coincidental, as there is emerging consensus that a more active, structured, and coherent treatment approach may be a common factor explaining the effectiveness of evidence-based treatments of BPD [32]. As outlined in detail in this chapter, a more active interpersonal, supportive, and structured approach is central to MBT.

The Relationship Between BPD and Depression

The precise nature of the relationship between depression and BPD is elusive. This should come as no surprise, as depression refers to (a) a psychobiological response to loss and defeat, (b) a symptom, and (c) a disorder [23]. BPD, in turn, has not quite shed its historic definitional challenge of being an "adjective in search of a noun" [33].

As is well known, BPD has been conceptualized as (a) a level of functioning [34, 35] encompassing a wide variety of personality disorders; (b) a disorder with substantial overlap/comorbidity with other disorders such as substance abuse disorder, posttraumatic stress disorder (PTSD), and mood disorders [36, 37]; and (c) part of a spectrum of affective disorders (including bipolar disorder)—given its high comorbidity with mood disorders [38]—congruent with models of BPD that emphasize affect dysregulation, and depression in particular, as a key feature of BPD [39]. Yet, BPD has also been hypothesized to be (d) part of a spectrum of psychotic disorders; [40] and (e) part of a spectrum of PTSD [41].

A focus on descriptive diagnostic criteria and features alone may not shed further light on these issues [42], as disturbed mood is essential to BPD and, conversely, disturbed interpersonal relationships have been implicated as a cause, concomitant, and consequence of depression [22]. This is also shown by rather unproductive attempts to decrease the comorbidity between BPD and mood disorders by replacing the word "depression" in the DSM-III-R criteria with the word "dysphoria." While these efforts to distinguish phenomenologically between feelings of depression in MDD and BPD are, as we explain in more detail below, legitimate, they are unlikely to resolve matters, as studies suggest that BPD is most distinctly characterized by *affective dysregulation* or *affective instability* rather than dysphoria [36]. If the core problem of BPD includes instability of affect states, then studies investigating longitudinal relationships between MDD and BPD, although informative, will similarly be limited in their ability to shed light on the relationship between mood problems and BPD.

From our attachment theory and mentalizing perspective, the possibility of untangling the Gordian knot of the relationship between depression and BPD lies in analyzing the differences in the developmental pathways involved in patients with depression with and without BPD features. Developmental factors moderate differences in symptomatology, phenomenology, prognosis, and treatment response. Also congruent with this emphasis on developmental continuities is a dimensional approach to pathology intrinsic to the NIMH's Research Domain Criteria (RDoC) initiative [43]. Our focus is on the role of the behavioral and neurobiological aspects of attachment and mentalizing (social cognition) in generating the developmental pathways that are implicated in mood disorders and BPD. Given this focus, differences between mood disorders and BPD are unlikely to be categorical, but the differences in developmental behavioral paths and underlying neurobiology are sufficient to warrant separate consideration, particularly as they have important but specific treatment implications.

The Mentalizing Approach to BPD and Mood Disorders

Similarities Between BPD and Mood Disorders

BPD and depression are not only highly comorbid at the symptomatic and syndrome levels; there is also increasing evidence for shared underlying psychosocial and neurobiological mechanisms. From the mentalizing perspective, findings

concerning the powerful ties between disruptions in (a) mentalizing and attachment experiences and (b) stress/affect regulation in mood disorders and BPD [41, 44] are crucial here. We discuss these findings and highlight commonalities between mood disorders and BPD.

Disruptions in Mentalizing and Attachment

The *mentalizing* approach originally developed in an attempt to understand patients with marked borderline pathology and their difficulties in reflecting on the self and others, specifically in attachment contexts [45, 46]. In these circumstances, these patients tend to lose the capacity for more controlled, reflective functioning concerning the self, others, and the relationship between the self and others and to switch increasingly to so-called nonmentalizing modes of experiencing subjectivity. These primitive, pre-mentalizing modes of function include *psychic equivalence* (in which mental events are considered to have the same status as physical reality), *teleological thinking* (the assumption that emotional difficulties can be solved by doing; for instance, anger can be resolved by destruction of property or violence), and *pretend mode* (when subjectivity becomes completely separated from reality and mentalizing becomes excessive but lacking in depth and genuine meaning).

Mentalizing has the function of maintaining an illusion of self-integration or self-coherence by linking observed acts and experiences to plausible intentional states [47]. Because of the fragmentation of the self that results from the use of nonmentalizing modes, BPD patients are often characterized by a tendency to externalize "alien-self" parts, which are felt to threaten the self from within, in an attempt to restore coherence in the self-experience [48]. This need to externalize may be expressed in acting-out behavior, self-harm, and/or a tendency to coerce others into specific roles (i.e., that of the one who neglects, abandons, or criticizes the patient). Studies increasingly suggest [49] that this tendency might be rooted in disturbed attachment relationships and attachment trauma in particular in interaction with biological predisposition [50, 51].

There is good evidence to suggest that both depression and BPD are associated with impairments in mentalizing and in the neural circuits that are implicated in mentalizing [49, 52], including the medial prefrontal cortex, amygdala, hippocampus, and ventromedial parts of the basal ganglia [53–55]. Moreover, these dysfunctions have been linked to failure of top-down regulation and/or impairments in bottom-up input, reflecting hypersensitivity of limbic structures that in concert may be responsible for the impairments in autonomic regulation, emotion regulation, and neuroendocrine stress responses typically observed in mood disorder [53–55] and, in more extreme forms, in BPD [49].

The link between these formulations of the features typical of patients with BPD and patients with mood disturbances is obvious: many BPD patients suffer from mood problems because of *attachment disruptions* and resulting problems in self-esteem; and these issues are easily reactivated by current stress and arousal, particularly in interpersonal relationships. Mood problems further impair mentalizing,

leading to a vicious cycle characterized by hypervigilance to rejection/abandonment and increasing depression. Similarly, hypersensitivity to experiences of failure (either real or imagined), which has also been implicated in vulnerability to depression [56], trigger feelings of being unloved and unwanted [6], a feature typical of BPD patients.

Depression can thus be seen as a basic psychobiological reaction to experiences of (anticipated) loss and separation [57], either directly through the threat of loss and abandonment or indirectly through experiences of failure [58]. As such, depression can be expected to be central in BPD. Strong rejection sensitivity is indeed typical of BPD patients and has even been conceptualized as the interpersonal phenotype of BPD [44, 59]. Similarly, self-criticism (e.g., evaluation of the emotional self as characterized by unworthiness, inferiority, failure, guilt, and chronic fear of disapproval and rejection) is a key part of BPD [56]. Blatt and colleagues have argued in this context that problems concerning rejection sensitivity and dependency can be situated on a continuum ranging from more psychotic to more high-functioning histrionic levels of functioning [60]. The importance of mood problems in BPD, and thus comorbidity between mood disorders and BPD, should thus not surprise us. Recently, negative self-referential processing in combination with emotionality has been suggested to be an endophenotype of treatment-refractory patients who fail to achieve a satisfactory treatment response [61, 62].

In an attempt to regulate increasing levels of arousal (including depressed mood), individuals may begin to rely on secondary attachment strategies (i.e., attachment hyperactivating and deactivating strategies). This will likely bring about further limitations in mentalizing with regard to both one's own and other people's motivations and desires [63]. Increasing levels of depressed mood lead to further increases in arousal and stress levels, resulting in impairments and distortions in mentalization, which in turn lead to a loss of resilience in the face of stress and to a vicious cycle of increasingly depressed mood.

Congruent with these assumptions, insecure attachment has been related to vulnerability to both depression and BPD in children, adolescents, and adults [49, 64, 65]. Thus, both disorders share important developmental features. Likewise, research indicates that vulnerability to both depression and BPD is associated with personality traits or cognitive–affective schemas that are rooted in disruptive attachment experiences, notably interpersonal dependency and self-critical perfectionism [66–69]. Insecure attachment also prospectively predicts recurrent depression, more depressive episodes and residual symptoms, longer use of antidepressants, impairments in social functioning [70], and suicide [65].

The central role of attachment experiences in the causation of depression and BPD is further emphasized by findings concerning the central importance of *developmental adversity* and disruptive attachment experiences (in particular abuse and neglect) in the etiology of both disorders [41, 71], leading to a dysregulation of stress and affect regulation systems.

Disruptions in Stress and Affect Regulation

Early adversity has profound effects on the developing stress system; indeed, studies suggest that attachment experiences play a key role in the developing stress system [6, 72, 73]. Secure attachment experiences seem to buffer the effects of stress in early development, leading to a so-called "adaptive hypoactivity" of the hypothalamic–pituitary–adrenal (HPA) axis in early development and to resilience in the face of adversity in later life [74]. By contrast, research [73–77] shows that insecure attachment experiences are associated with increased vulnerability to stress, as expressed, for instance, in HPA axis dysfunctions.

Together, these findings may at least partially explain the mounting evidence that vulnerability to depression is associated with an *increased stress response* to both daily and major life stressors [41, 78], explaining, at least in part, high comorbidity and overlap with BPD. Several studies do indeed suggest that insecure attachment experiences mediate the relationship between early adversity and vulnerability to depression through *impaired affect regulation, stress responsivity*, and *social problem-solving skills* [79, 80]—features that are also typical of BPD patients [81].

Moreover, although the evidence is still somewhat equivocal [82], there is some evidence that increased stress responsivity as a result of early or later adversity is particularly pronounced in individuals with genetic liability, which might also be the case in BPD [50]. For instance, studies suggest that a polymorphism of the 5HTT gene may be associated with increased stress sensitivity, resulting in increased vulnerability to depression [82] as well as BPD, although recent meta-analyses have called these findings into question [82, 83].

There is now also evidence [75, 76, 84–86] that the neuropeptides oxytocin and vasopressin, which are involved in neural systems underlying attachment [76, 87], play a key role in disrupted stress regulation in mood disorders and BPD. Oxytocin plays a role in affiliative behavior (including pair bonding, maternal care, and sexual behavior) as well as in social cognition [88, 89] and in reducing behavioral and neuroendocrinological responses to stress [76].

Early adverse attachment experiences are associated with decreased oxytocin levels and increased cortisol response [41, 90, 91]. High levels of attachment anxiety and avoidance have been associated with polymorphisms in the oxytocin receptor gene in patients with unipolar depression [92], and studies have also found dysregulated peripheral oxytocin release in depressed women [93]. Gotlib and colleagues reported that adolescent girls who were at risk for depression showed decreased activation in the reward processing system (and particularly striatal areas), suggesting a marked reduced sensitivity to reward [94]. Similarly, low endogenous levels of oxytocin, polymorphisms in oxytocin-related genes, and negative (instead of positive) effects of oxytocin administration have also been documented in BPD [93, 95–97]. These findings suggest at least some overlap between depression and BPD in terms of a dysfunction of the oxytocinergic system (underlying attachment behavior and stress regulation), which may also explain the inverse effects of oxytocin administration in these patients [98].

What Then Is the Difference?

Although patients with depression with and without BPD features probably need to be situated on a continuum with regard to underlying psychosocial and neurobiological mechanisms, at least four related differences seem to distinguish these groups of patients: (a) *the nature of depressive experiences*; (b) *the nature of mentalizing deficits*, which are more extreme in BPD patients in terms of both intensity and content; (c) *the nature of attachment experiences*, with BPD patients showing more disorganized attachment features as a result of more severe disruptions of the attachment system (which may be in part related to genetic as well as environmental factors); and (d) the profound loss of mentalizing in BPD patients, which, coupled with disorganized attachment features, typically leads, in the psychic equivalence mode, to strong and painful feelings of emptiness/lack of meaning. As a result, this intensifies feelings of identity diffusion and hypersensitivity to rejection and increases pressure to externalize alien-self parts in a teleological attempt to get rid of these feelings. These tendencies, in our opinion, lead to a profound lack of *epistemic trust* and an *epistemic hypervigilance*, which necessitates a different treatment approach, as these features seriously threaten the ability to form a working alliance, and these patients typically lack the reflective capacities that are needed in many current evidence-based treatments for depression. We review each of these issues in more detail below.

When Depression Is Not Just Depression

More than 20 years ago, Drew Westen and colleagues noted that "depression is not just depression" in BPD patients [3]. Indeed, studies since have amply demonstrated the phenomenologically very different nature of depression in BPD patients. Patients with marked BPD features have greater affective instability (which makes the relationship between stressful experiences and the onset of depression, so typical of depressed patients without such features, less obvious in BPD patients) [69]. Studies also suggest that patients with BPD features also have a greater painfulness of depressive experiences as evidenced by higher scores on self-report, but not observation-based, measures of depression [4, 99, 100]; more feelings of emptiness and diffuse negative affectivity [3]; higher levels of self-criticism [101, 102]; and a greater focus on fears of abandonment [4, 103] and shame [104, 105], which predict self-destructive behaviors, impulsivity, and interpersonal distress [4, 106].

Profound Mentalizing Impairments

From a phenomenological perspective, depression in patients with marked BPD features reflects a more severely nonmentalizing way of experiencing subjectivity as compared to depressed patients without such features. There are differences in intensity, but these also reflect differences in the quality (i.e., content) of

mentalizing failures, which may have etiological underpinnings. Because of the ready loss of mentalizing in BPD patients, feelings of rejection and abandonment, in a *psychic equivalence* mode, can feel extremely painful in these patients. Feelings of unattractiveness are felt as an absolute truth. Zanarini and colleagues [100] noted this aspect of BPD phenomenology. We have attributed this to an underlying disorganization of the self, rooted in disorganized attachment and leading to alien-self experiences (e.g., "critical introjects") and the risk that increasing incoherence of the self generates stronger pressure to externalize (project and attribute to others) the alien-self experience [107]. Greater self-harm and destructiveness may result, and these features also negatively influence the therapeutic relationship as therapists are more likely to become entangled in difficult transference–countertransference relationships [108–110].

The so-called depressive realism often reflects a more accurate and less rose-colored view of reality in those with depression without marked BPD features [111, 112]. In BPD patients, "depressive realism" shifts into psychic equivalence and often borders on the complete absence of an experience of symbolic representations, or hypomentalizing: there is really nothing that is worth living for; the self feels completely empty, unattractive, and unworthy.

Disturbed mood further impairs individuals' ability to mentalize. When the individual is depressed, mentalizing is likely to be distorted for both MDD and BPD patients, but in the latter group, depression can trigger the reemergence—either temporarily or more chronically—of modes of thinking that antedate full mentalizing, which can lead BPD patients to devalue the significance of subjective experience and prioritize physically observable outcomes (teleology, or judging experience solely by its physical outcomes). The loss of mentalizing leads patients to feel unable to accept anything other than a modification in the realm of the physical as a true index of the intentions of the other. This may be linked to the extreme focus on exterior indicators of mental states (such as gestures and expressions). The weight of evidence suggests that mentalizing tasks that focus attention on external features cause fewer problems for these patients; indeed, BPD patients have been found to be hypersensitive to facial expressions [113–115].

The ease with which BPD patients can lose reflective, controlled mentalizing probably also contributes to the ready emergence of a *teleological mode* of thinking. The failure of reflective mentalizing in BPD has been repeatedly demonstrated using attachment narratives [116–118] and has been shown to be reversible by psychotherapy [119]. Other studies have shown BPD patients to be impaired on the Movie for the Assessment of Social Cognition (MASC), a video-based test of mentalizing which requires participants to recognize the mental state of characters as they interact in an everyday life group scenario involving relationships [120–122]. In patients with marked BPD features, a teleological stance often leads to frantic attempts to get attachment figures, including the therapist, to show that they care, like, and love the patient. Hence, patients may demand longer or more sessions and, in more extreme cases, demand to be touched, caressed, or hugged by their therapist, which may lead to boundary violations. While this can also occur in depressed patients without marked BPD features, such tendencies are mostly understood to be "not for real."

In psychic equivalence and the teleological mode of functioning, the subjective experience is one where the implication of failing to achieve the physical outcome is catastrophic and can feel like a choice between life and death. Suicidal ideation deserves special attention here, particularly as studies suggest highly increased rates of suicidal behavior in depressed patients with BPD features. A recent population-based study, for instance, showed that comorbid BPD features were strongly associated with suicide attempts in patients with major depressive disorder [123]. Similarly, Stringer and colleagues showed, in a study of 1,838 depressed patients, that the suicide attempt rate ratio increased by a staggering 33 % for every unit increase in BPD features [1]. Sharp and colleagues showed that BPD features predicted suicidal ideation (and self-harm more generally) over and above major depressive disorder in a sample of 156 adolescents admitted to a specialized treatment setting [124].

The tendency to function in the teleological mode may explain the higher levels of impulsivity and aggression that make these patients more prone to suicidal behavior [1]. In the case of depressed patients without marked BPD features, thoughts and feelings concerning suicide are more embedded within an interpersonal context that is more readily available to the patients, with suicidal thoughts involving harsh self-criticism and anger turned toward the self, fantasies about killing hated parts of the self, and omnipotent fantasies about reunion with lost loved ones. In the case of depression and suicidal tendencies in BPD patients, these interpersonal links are less clear to the patient, and it often seems to be the "too realness" of painful inner states (feelings and emotions) that primarily leads patients to ideas or acts of suicide in an attempt to silence inner feelings of pain.

A feature of BPD phenomenology that distinguishes the condition from simple depression is hypermentalizing. Hypomentalizing, particularly in BPD patients, is often followed by *extreme pretend mode* or *hypermentalizing accounts* in which the relation to reality is severed [122, 125]. In the pretend mode, ideas form no bridge between inner and outer reality; the mental world is no longer fully coupled with external reality; explicit mentalizing has been overridden by implicit mentalizing; an excessive internal focus is unchecked by reference to external indicators; there is poor belief–desire reasoning, vulnerability to fusion with others' identity, and a tendency to become lost in the complexity of the world of beliefs and desires with which physical reality is only loosely coupled. In hypermentalizing, groundless inferences are made about mental states, sometimes reminiscent of confabulation [122, 126]. Hypermentalizing accounts of interpersonal events often strike the clinician as overly analytical, repetitive, and lengthy in nature, colored by depressive themes (e.g., guilt and shame). In BPD patients, hypermentalizing accounts are typically more self-serving (e.g., to receive attention or compassion or to control or coerce others) and affectively overwhelming interpersonal accounts that often lack coherence. Mentalizing impairments in depressed patients with marked BPD features manifest in extreme hypermentalization–hypomentalization cycles.

The limitations of mentalizing may account for the need for long-term interventions for BPD [127], in contrast to the effectiveness of a range of short-term therapies for MDD patients [128]. We would argue that mentalizing deficits can generate

problems in the formation of therapeutic alliances in treatments of BPD patients [129, 130]. Brief, focused treatment packages assume a capacity for insight and reflectiveness that is likely to exceed the patients' abilities to mentalize effectively, particularly under conditions of arousal. Increased arousal could further disrupt the possibility of effective higher-order cognitive function.

If therapy activates the attachment system, which in turn increases the risk of interpersonal misunderstanding, there will be a risk of getting into a vicious cycle of increasing self-criticism, rumination, helplessness, and suicidal thoughts. We have consistently argued that in order for BPD patients to benefit from psychotherapy, the initial focus must be on the recovery of mentalization, which provides the necessary basis for the patient to engage in a reflective psychological process [32, 131]. Depressed patients with marked BPD features (and chronic depressed patients more generally, many of whom have BPD features) thus seem to have lost the "self-righting tendency" that is associated with the capacity for controlled mentalizing.

Attachment in BPD and Mood Disorders

This brings us to attachment issues. We believe that the typical features of depression in those individuals with marked BPD features are related to a *disorganization* of the attachment system, rather than the organized insecure attachment strategies that are typical of depressed patients without marked BPD comorbidity. Whereas *organized* types of insecure attachment (i.e., anxious–ambivalent and anxious–avoidant) reflect relatively stable ways of dealing with stress and arousal (i.e., respectively, using predominantly attachment hyperactivating and deactivating strategies), individuals with *disorganized* attachment often show marked variability in the use of attachment hyperactivating and hypoactivating strategies, reflecting a lack of a coherent, organized attachment strategy when faced with increasing stress and arousal [132]. Studies suggest that for these individuals, the caregiver has served as a source of both fear and reassurance, so that activation of the attachment system produces strong conflicting motivations. Research has found that histories of prolonged or repeated separation [133], intense marital conflict [134], and/or severe neglect or physical or sexual abuse are often associated with this pattern of attachment [135], although the evidence linking such developmental histories to BPD longitudinally is still quite limited. However, studies do suggest that frightened or frightening states of mind [136] in attachment figures prospectively predict BPD features. Lyons-Ruth and colleagues, for instance, found that such severely disrupted maternal communication and maltreatment were independent predictors of BPD symptoms at age 18 [137]. Early separation from the primary caregiver has been found to predict a slower decline of BPD scores through adolescence [138]. The role of disorganized attachment in BPD may account for (a) the often-noted fears of abuse that are triggered by attachment relationships in these individuals, (b) the fact that their attachment system is extremely readily activated, and (c) that while they seem constantly preoccupied with attachment relationships, they tend also to engage in idealization–denigration and push–pull cycles in relationships.

Few studies have compared attachment in depressed patients with and without marked BPD comorbidity [6], and existing studies on attachment in depression often fail to control for comorbidity with BPD and trauma. In an unusual study, Choi-Kain and colleagues [139] showed that patients with mood disorder could be differentiated from those with BPD in terms of attachment style, even on self-report questionnaires, consistent with the case being built here. Both MDD and BPD patients showed greater preoccupation and fearfulness than community controls, in agreement with other studies that have found higher levels of insecure attachment (and particularly organized insecure attachment styles) in patients with MDD [64, 70, 80, 140, 141]. However, BPD patients had higher levels of both preoccupation and fearfulness, and only patients with BPD simultaneously showed preoccupation *and* fearfulness. These findings suggest more profound disruptions of attachment in BPD than MDD patients and may be indicative of the lack of any functional regulation strategy to reduce attachment distress that we have hypothesized [45, 142, 143]. These assumptions are further supported by the findings by Shedler, Westen, and colleagues with the Shedler–Westen Assessment Procedure (SWAP); based on clinician ratings, they found that a borderline-dysregulated spectrum emerged as a separate and coherent personality prototype characterized by strong fears of rejection, abandonment, and isolation and by becoming attached quickly and intensely [144].

Attachment and Epistemic Trust/Hypervigilance

Finally, more recently, we have argued on the basis of pioneering work by Sperber [7, 145] and Corriveau et al. [146] that secure attachment experiences pave the way not only for the acquisition of mentalizing but also, more generally, for the formation of "epistemic trust," defined as an individual's willingness to consider communication conveying new knowledge from someone as trustworthy, generalizable, and relevant to the self [9]. Corriveau's study demonstrated that attachment security increased the likelihood of an infant trusting the reliability of a communication source when it was reasonably credible, while preoccupied and anxiously attached children over-relied on the views of the attachment figure (mother) in an ambiguous situation [146]. The latter pattern could be considered the consequence of a kind of *epistemic dependency*, in which the child has developed a chronic lack of confidence in their own understanding. While secure attachment empowered a child's confidence in their own experience, beliefs, and judgment, an avoidant attachment history was associated with epistemic mistrust, leading to a tendency for the child to reject even plausible information from the attachment figure and an increased likelihood of accepting the information coming from a stranger. Finally, disorganized attachment, rooted presumably in a history of misattunement, led to mistrust of information from both attachment figures and strangers.

It seems to us that attachment disorganization therefore leaves the individual in a terrible quandary about "whom to trust?" The person whose insecure attachment history precludes confidence in their own experiences and beliefs is left in a

permanent and irresolvable state of epistemic searching. They seek others to confirm or deny their own understanding, but they are also not able to trust the information they receive, ultimately generating a state of epistemic hypervigilance. While organized insecure attachment styles can be associated with either considerable epistemic mistrust (in the case of avoidant attachment) or excessive trust (in the case of preoccupied–anxious attachment), we believe that disorganized attachment is associated, particularly in attachment contexts, with a confusing combination of *low epistemic trust* and *epistemic dependency*, leading to marked *epistemic hypervigilance*. Of course, such a disorganized state would place serious limits on these patients' capacity to benefit from more insight-oriented psychotherapeutic approaches.

Within the therapeutic context, the particular and profound difficulties in communication that arise from epistemic hypervigilance often give the BPD patient a peculiarly rigid and unreachable quality, often leading to intense feelings of frustration on the part of the therapist. It is now to the question of how mentalization-based treatments can serve to reach patients with mood disorders with marked features of BPD that we will turn.

Implications for Treatment

A Spectrum of Mentalization-Based Interventions

Throughout this chapter, we have argued that a mental representation model that relies heavily on reflective capacities is less appropriate in the treatment of BPD patients and mood problems in the context of BPD and might even be associated with iatrogenic effects. Given the greater propensity to revert to nonmentalizing modes, with increasing pressures to externalize alien-self parts, and their often profound levels of epistemic hypervigilance, these patients are unable to form the kind of working alliance that is typically required in these treatment models. Structured interventions (and brief interventions in particular) for depression rely upon capacities for relating to the therapist and for insight that these patients simply do not possess. Indeed, many current treatment models for depression are based on the premise that the patient has the capacity for epistemic trust or that this capacity, at the very least, can be reactivated relatively easily. In patients who largely lack epistemic trust, a mental process focus is indicated. Yet, as noted, patients with less comorbidity in terms of BPD pathology may also benefit from a mentalizing or metacognitive focus, as is also demonstrated by studies demonstrating the effectiveness of mindfulness-based approaches in patients with mood disorders, although it must be said that these approaches seem particularly effective in chronically depressed patients, many of whom probably have comorbid personality pathology [6, 147, 148]. In patients with greater epistemic trust, a mental process focus may be easier to combine with a mental representation focus and with the use of more "traditional" expressive techniques.

Over the past years, together with a number of colleagues, we have developed Dynamic Interpersonal Therapy (DIT), a treatment model that combines both perspectives. DIT illustrates how a combination of a mental representation and mental process approach may be used in a brief treatment format aimed at treating depressed patients who may have some, but not marked, BPD features. For the more severe spectrum of depressed patients with marked BPD features, Mentalization-Based Treatment (MBT) for BPD might be more indicated. When working with patients with BPD features, the first task at hand is often to establish a trusting relationship that can be the basis for exploring the influence of mental states on mood, something that is taken for granted in many treatment models for depression.

Dynamic Interpersonal Therapy for Depression

DIT is an integrative treatment that represents a distillation of evidence-based brief psychoanalytic/psychodynamic treatment models [5, 149]. DIT incorporates a mental representation and a mentalizing approach. With regard to the first of these, this is done by taking a so-called Interpersonal Affective Focus (IPAF) as the focus of the treatment. More traditional supportive and expressive techniques are used to develop this focus in interaction with the patient and to work it through. DIT also includes a strong mentalizing focus, using more directive and mentalizing interventions to increase reflective capacities in the patient. Hence, rather than focusing on content, a focus on fostering reflective processes is often thought to be equally if not more effective in DIT. Similarly, transference interpretations are limited and are mainly made in order to clarify the IPAF, particularly in patients who have a strong transference response (which, if unaddressed, hampers the therapeutic process). The use of the transference in DIT is also appropriate when patients have few interpersonal relationships, and thus the therapeutic relationship becomes an important vehicle to identify and work through the IPAF.

This is congruent with studies that show a negative relationship between a high frequency of transference interpretations and both the therapeutic relationship and outcome in brief and long-term psychoanalytic treatment, even in patients with high levels of personality functioning [150]. A study by Hoglend and colleagues [151, 152], for instance, found no differences in the efficacy of two psychodynamic treatments that differed only in terms of the use of transference interpretation (i.e., with and without the use of such interpretations) both at treatment termination and at 3-year follow-up, except in patients with low levels of personality functioning. These patients responded better to treatment with a low frequency of transference interpretations (0–3 per session) compared to treatment without transference interpretations. Moreover, in these patients, increases in insight mediated the relationship between transference interpretations and improvements in relational functioning [153]. Hence, transference interpretations may be a "high-risk/high-gain" strategy in relation to patients with (marked) BPD features: they may lead to increased insight but also increased defensiveness and disturbances of the therapeutic

relationship and the therapeutic process [154]. The other important implication from this study is that, in patients with higher levels of functioning, a more general interpersonal focus that does not use transference interpretations is as effective. These findings provide further confirmation, in our opinion, of the need to address the immediacy and strong nature of attachment imperatives (and subjective experiences more generally)—fuelled by epistemic hypervigilance and attachment disorganization—in patients with (marked) BPD features. In patients with more epistemic trust, as in patients with organized insecure attachment features, such a focus is less intensely required.

Similarly, while past experiences and their influence on current functioning are acknowledged in DIT, they are not the major focus. The focus is on the IPAF in DIT, that is, the patient's current interpersonal functioning as it relates to the presenting symptoms, keeping in mind that a discussion of past experiences, and particularly traumatic experience, may easily overwhelm patients' mentalizing capacities.

DIT is a time-limited (16 sessions) intervention that thus primarily targets the capacity for mentalizing (mental process focus) and connections between mood symptoms and interpersonal functioning (mental presentation focus).

DIT consists of three phases (initial, middle, and ending), each with specific aims and strategies. The primary task of the initial phase (sessions 1–4) is to identify one dominant and recurring unconscious interpersonal pattern, the IPAF, which is assumed to be central to the onset and/or maintenance of the depressive symptoms. This pattern is underpinned by a particular representation of self-in-relation-to-another that characterizes the patient's interpersonal style and leads to difficulties in his/her relationships. These representations are typically linked to particular affect(s) and defensive maneuvers. Affects are understood to be responses to the activation of a specific self—other representation in the patient's mind. This particular way of formulating derives from Kernberg's work [155] and is thus heavily influenced by mental representation models. For example, an IPAF might focus on a self-representation as "helpless victim" in relation to others who the individual feels constantly criticize and neglect him/her. The defensive function of this constellation is to defend against underlying feelings of frustration and aggression and to reverse the role and triumph over criticizing others. These patterns and their high (interpersonal) costs are highlighted, which leads the patient to relinquish these patterns. Hence, the focus on the IPAF combines a mental representation and mentalizing approach. In patients with marked impairments in mentalizing, interventions often address much more basic dynamics, such as (a) affect recognition and affect differentiation, (b) linking affect to depressed mood and anxiety, and (c) linking affect to the IPAF. Hence, both components—the mental representation and the mental process focus—allow the therapist to tailor his/her interventions to the specific mentalizing capacities within the session, with greater weight to mentalizing and supportive interventions in patients with BPD features.

The middle phase (sessions 5–12) involves (a) maintaining a focus on the agreed IPAF; (b) helping the patient to identify areas of difficulty in his/her relationships and understand his/her characteristic ways of managing these difficulties, pointing out the interpersonal "costs" of these strategies; (c) stimulating the patient's capacity

to think about and understand his/her thoughts and feelings (the mentalizing focus) and how these underpin strange or self-defeating behaviors and patterns of relating; (d) attending to the patient's affective state; (e) focusing on the therapeutic relationship as a live example of the IPAF in action; and (f) helping the patient practice the skill of recognizing internal states (feelings and thoughts, wishes, etc.) and connecting these to the week's events and to the IPAF. This phase may prove very difficult for patients with BPD features, as they may be easily overwhelmed by more interpretive work; thus, in these patients, a greater emphasis on support, validation, and mentalizing is needed. Often, it is very difficult to delineate a specific IPAF as the focus of treatment, as the IPAF (and thus the use of attachment hyperactivating and deactivating strategies) seems to change constantly. For instance, at the start of the treatment, the patient might present as a hopeless victim in the hands of others. This pattern might soon change to the opposite direction, only to then change back to the original pattern and so on, leading to confusion in both the patient and the therapist. This reflects, in our opinion, a disorganization of the attachment system that seriously impacts on the treatment process, as neither the patient nor the therapist is sure what exactly they are trying to address from a mental representation perspective—particularly as the patient typically lacks the capacity to simultaneously consider both patterns and their interrelationship. This should alert the clinician to the possibility that DIT may not be the treatment of choice for this patient.

The final phase (sessions 13–16) is devoted to helping the patient explore the affective experience and the conscious and unconscious meaning of the therapy ending, reviewing the progress made, and helping the patient to anticipate future difficulties or vulnerabilities. Work in these final sessions involves (a) systematically addressing the patient's feelings, unconscious fantasies, and anxieties about the termination of therapy; (b) responding to any signs of regression (e.g., a deterioration in the patient's symptoms) near the end of treatment by linking this with the patient's feelings and fantasies regarding endings; (c) helping the patient to review the therapy overall (e.g., whether he/she has achieved his/her initial aims); and (d) the therapist writing a "goodbye" letter for the patient, which sums up the original agreed formulation and what progress has been made in working on the issues identified in it.

Responses to the impending end of treatment are more likely to be more extreme in patients with BPD features, and therapists may be "seduced" by the patient to offer additional sessions as the approaching end of treatment generates abandonment anxieties and feelings of aggression in the patient, leading the therapist to increasingly worry about the patient. Again, a more validating approach is helpful here, and lowering the patient's level of arousal is needed before he/she can adopt a more reflective stance.

Although DIT is currently a manualized, short-term treatment, the techniques and principles used can be flexibly integrated with other (longer-term) treatments. Patients with more marked BPD features, in particular, may benefit from a longer, more open-ended treatment approach. This may focus in more detail on the relationship between current and past relationships and functioning and aim at more profound changes in character.

Earlier, we reviewed evidence suggesting that BPD features may impede treatment response in brief treatments. Whether this is also the case in DIT is ultimately an empirical question. Over the past decades, evidence for both more traditional intrapersonal and more interpersonal brief and long-term treatments in depression with and without comorbid personality pathology has been accumulating [156–160]. In line with these findings, a recent small pilot trial showed that DIT was associated with a significant reduction in symptoms in all but one case, to below clinical levels in 70 % of the patients studied [63]. Further research is needed to investigate the influence of BPD features on DIT. A large randomized trial is currently underway that will address these issues.

Mentalization-Based Treatment and Mood Problems in BPD Patients

MBT originated in the treatment of patients with BPD, many of whom struggle with intense and chronic feelings of depression [6]. The treatment evolved precisely out of dissatisfaction with more traditional, insight-oriented treatments, as these overestimate the mentalizing capacities of BPD patients. Here, we present the core principles and techniques of MBT, with a focus on depression in BPD. We also review preliminary evidence suggesting that MBT may be particularly effective in reducing depression in BPD.

The MBT approach is based on a view that a core problem for many patients, and typically those with BPD, is their vulnerability to a loss of mentalizing in combination with epistemic hypervigilance. MBT places mentalizing at the center of the therapeutic process. At its core is the argument that MBT works through the therapist establishing an enduring attachment relationship with the patient while continuously stimulating a mentalizing process in the patient.

The basic aim of the treatment is to reestablish mentalizing when it is lost and maintain mentalizing when it is present. Therapists are expected to focus on the patient's subjective sense of self. To do so, they need to (a) identify and work with the patient's mentalizing capacities, (b) represent internal states both in themselves and in the patient, (c) focus on these internal states, and (d) sustain this focus in the face of constant challenges by the patient over a significant period of time. In order to achieve this level of focus, mentalizing techniques need to be (a) offered in the context of an attachment relationship, (b) consistently applied over time, and (c) used to reinforce the therapist's capacity to retain mental closeness with the patient. Congruent with our assumption of severe attachment and mentalizing impairments in patients with BPD, which typically give rise to epistemic hypervigilance, MBT is manualized to facilitate the achievement of these primary goals and entails a strong focus on mentalization techniques while avoiding harm to a group of patients who may be particularly vulnerable to the negative effects of psychotherapeutic interventions. This may be particularly important when dealing with feelings of depression in patients with severe BPD features. As noted above, depressive

experiences in these patients are often marked by excessive feelings of self-criticism, emptiness, and meaninglessness and associated with a high risk of self-harm. In such states of mind, a focus on "insight," particularly when focused on events in the past and when combined with a more neutral and distant therapeutic stance, is at best unhelpful and at worst likely to be iatrogenic. The MBT approach therefore entails a titrated but more or less exclusive focus on the BPD patient's *current* mental state and with special attention paid to avoid generating iatrogenic effects, as this focus inevitably activates the attachment system. Hence, treatment should avoid situations where patients are expected to talk of mental states that they cannot link to subjectively felt reality; this is particularly important when speaking about depressive experiences. When feeling depressed, BPD patients all too readily revert to psychic equivalence mode, rendering depressed feelings even more painful and real, or to an extreme pretend mode, leading to profound feelings of helplessness and self-criticism. Thus, the MBT approach involves (a) a de-emphasis of "deep" unconscious interpretations in favor of conscious or near-conscious content addressing the here and now (e.g., "what happened just now that you feel like this?"); (b) a modification of the therapeutic aim, especially with severely disturbed patients, from insight to recovery of mentalization (i.e., achieving representational coherence and integration) (e.g., "I can see that you feel rejected, but let us pause and reflect for a minute on what just happened, and what he could have meant by saying that to you"); (c) careful avoidance of the use of descriptions of complex mental states (e.g., conflict, ambivalence, unconscious) that are incomprehensible to a person whose mentalizing is vulnerable and instead sticking to the here and now or "working memory"; and (d) avoidance of extensive discussion of past trauma except in the context of reflecting on the patient's current perceptions of the mental states of maltreating figures and changes in their own mental state from being a victim in the past versus their experiences now. As noted, patients with BPD features often tend to dwell on traumatic experiences in the past, especially when depressed; this can lead to hypomentalizing–hypermentalizing cycles ("I am abused, I am bad, there is nothing that anyone can do about this, I am beyond help—what if this never happened, if he hadn't done that to me, my life could have looked completely different; I often think about this, and it tends to drive me crazy, it is all so painful"). These cycles tend to spiral out of control and lead, in a teleological mode, to increasing thoughts about self-harm and/or suicidality. Hence, in MBT, instead of encouraging the patient to explore such thoughts further, he/she is redirected toward exploring the influence of these thoughts on current thoughts and feelings and/or their relation to current events.

The theoretical model proposed in this chapter also implies that in order to maximize the impact on the (depressed) patient's ability to think about thoughts and feelings in relationship contexts, especially in the early phases of treatment, the therapist is probably most helpful when his/her interventions (a) are simple and easy to understand, (b) are affect focused, (c) actively engage the patient, (d) focus on the patient's mind rather than on his/her behavior, (e) relate to a current event or activity, whatever is the patient's currently felt mental reality (in working memory), (f) make use of the therapist's own mind as a model (e.g., by the therapist disclosing

his/her anticipated reaction in response to the event being discussed, i.e., talking to the patient about how the therapist anticipates that he/she might react in the same situation), and (g) are flexibly adjusted in complexity and emotional intensity in response to the intensity of the patient's emotional arousal (i.e., withdrawing when arousal and attachment are strongly activated).

The key task of therapy is thus to promote curiosity about the way mental states motivate and explain the actions of self and others, *even* in depressed states of mind (i.e., "finding meaning and coherence where none is felt or expected"). Therapists achieve this through the judicious use of the "inquisitive stance," in which they highlight their own interest in the mental states underpinning behavior, qualify their own understanding and inferences (and show respect for the opaqueness in mental states), and demonstrate how such information can help the patient to make sense of his/her experiences. This inquisitive yet "not-knowing" stance is often exactly the opposite of the depressed patient's state of mind, which is characterized by a lack of curiosity to explore mental states or excessive certainty about mental states of the self and others. Pseudomentalization and other fillers that are particularly characteristic of depressed states (e.g., "All previous treatments have failed, I am a patient who does not respond to any treatment, nobody knows what to do with me"), and which replace genuine mentalization, must be explicitly identified by the therapist, and the lack of practical success associated with them should be clearly explained ("Well, I can see how you feel, and I can begin to understand why you feel like that, but it is not really helping us today, as you yourself said that these feelings drag you down"). In this way, MBT therapists can help their patients to learn about how they think and feel about themselves and others, how their thoughts and feelings shape their responses to others, and how "errors" in understanding self and others may lead to inappropriate actions.

Hence, working with depressed mood in MBT typically entails the following sequence, which closely follows the more general MBT approach: (a) the therapist identifies a break in mentalizing (described above as psychic equivalence, pretend mode, or teleological mode of thought) as a result of depressed mood ("I feel so helpless, everything I do is bound to fail, I cannot see where this is leading us"); (b) the patient and therapist "rewind" to the moment before the break in subjective continuity ("What happened just now so that you feel like that – is it related to something that I said?"); (c) the current emotional context for the break is explored by identifying the momentary affective state between patient and therapist ("You started talking about your job, and this is what seems to have happened, you became very self-critical"); (d) the therapist explicitly identifies and acknowledges their own contribution to the break in mentalizing ("Is it related to something that I said or did?"); and (e) the therapist seeks to help the patient understand the mental states implicit in the current state of the patient–therapist relationship (to *mentalize the transference*) ("When you said that, I started to feel helpless as well").

The therapist's mentalizing therapeutic stance throughout this process should include (a) humility deriving from a sense of "not knowing" ("Well, I can see that you feel helpless now, but I want to understand why that is, because I am concerned about you and why you feel like that"); (b) whenever possible, taking time to identify

differences in perspectives ("Well, you seem very sure that he said that to hurt you, but there may perhaps be other reasons for him saying that"); (c) legitimizing and accepting such different perspectives ("I now can see why you thought that but can you accept that he may have meant something different?"); (d) active questioning of the patient in relation to his/her experience, asking for detailed *descriptions* of experience ("what" questions) rather than *explanations* ("why" questions) ("So what did you feel then?"); and (e) eschewing the need to understand what makes no sense (i.e., saying explicitly that something is unclear) ("Sorry, but you lost me there").

An important component of the mentalizing stance is the therapist monitoring his/her own mistakes and owning up to them. This not only models honesty and courage through such acknowledgments and tends to lower the patient's arousal through the therapist taking responsibility, but it also offers valuable opportunities to explore how mistakes can arise out of inaccurate assumptions about mental states, which are opaque, and how such misunderstandings can lead to massively aversive experiences. Importantly, through "staying with the patient" even when the patient feels completely helpless and hopeless, a sense of concern and controllability is communicated—that is, that these states of mind are not as threatening, uncontrollable, and meaningless as they seem.

In this context, it is important to be aware that the therapist is constantly at risk of losing his/her capacity to mentalize in the face of a nonmentalizing patient. Especially when the patient is severely depressed, the therapist can feel as if they are being "sucked into a black hole," leading to hypomentalizing; alternatively, the therapist may be in such a state of high arousal, for example, because of the patient's threats to self-harm, that she/he feels compelled to intervene teleologically (e.g., by prescribing medication or having the patient hospitalized). Consequently, we consider therapists' occasional enactments as an acceptable concomitant of the therapeutic alliance and something that simply has to be owned up to. As with other instances of breaks in mentalizing, such incidents require that the process is "rewound" and the incident explored. Hence, in this collaborative patient–therapist relationship, both partners involved have a joint responsibility to understand such enactments.

Research evidence for the effectiveness of MBT for the treatment of BPD, including depression in BPD, is consolidating. A follow-up study of BPD patients 5 years after all treatment was complete (and 8 years after initial entry into treatment) compared patients who had been treated with MBT versus those who received treatment as usual (TAU) and found that those who received MBT remained better than the TAU group. Superior levels of improvement were shown for diagnostic status (13 % vs. 87 %), service use (2 years vs. 3.5 years), and other measurements such as use of medication, global function, and vocational status. Importantly, MBT was also superior in reducing levels of suicidality (23 % in the MBT group vs. 74 % in the TAU group) [161] and in reducing the severity of depression as assessed with the Beck Depression Inventory (unpublished data).

In relation to adolescence and the emergence of BPD traits, a more recent study by Rossouw and Fonagy [162] comparing the effectiveness of a version of MBT devel-

oped specifically for adolescents (MBT-A) in adolescents who self-harm against TAU found that MBT-A was more effective in reducing both self-harm behavior and depression. The improvements generated by MBT-A appear to have been mediated by improved levels of mentalization, reduced attachment avoidance, and amelioration of their emergent BPD features: individuals in the MBT-A group showed a recovery rate of 44 %, compared to 17 % in the TAU group.

Conclusions

This chapter has presented a mentalizing approach to mood problems and BPD. We consider patients with BPD and mood problems to be situated on a continuum. However, four related features seem to distinguish, in relative terms, individuals with mood problems with and without marked BPD features: (a) the nature of their depressive experiences; (b) the severity of their mentalizing impairments and particularly the extent to which they feel pressured to externalize alien-self parts; (c) insecure, but organized, attachment in response to stress and arousal versus disorganized attachment; and (d) problems with epistemic trust versus epistemic hypervigilance. We described DIT, a manualized treatment for depressed patients without marked BPD features that combines a mental representation and mental process focus that can be flexibly tailored to individual patients. For patients with more marked BPD features, more traditional and longer-term MBT might be indicated, as a result of the more marked impairments in mentalizing, attachment, and high levels of epistemic hypervigilance in these patients.

References

1. Stringer B, van Meijel B, Eikelenboom M, Koekkoek B, Licht CM, Kerkhof AJ, et al. Recurrent suicide attempts in patients with depressive and anxiety disorders: the role of borderline personality traits. J Affect Disord. 2013;151(1):23–30. doi:10.1016/j.jad.2013.02.038.
2. Levenson JC, Wallace ML, Fournier JC, Rucci P, Frank E. The role of personality pathology in depression treatment outcome with psychotherapy and pharmacotherapy. J Consult Clin Psychol. 2012;80(5):719–29. doi:10.1037/a0029396.
3. Westen D, Moses MJ, Silk KR, Lohr NE, Cohen R, Segal H. Quality of depressive experience in borderline personality disorder and major depression: when depression is not just depression. J Pers Disord. 1992;6(4):382–93.
4. Levy KN, Edell WS, McGlashan TH. Depressive experiences in inpatients with borderline personality disorder. Psychiatr Q. 2007;78(2):129–43. doi:10.1007/s11126-006-9033-8.
5. Lemma A, Target M, Fonagy P. Brief dynamic interpersonal therapy. A clinician's guide. Oxford: Oxford University Press; 2011.
6. Luyten P, Fonagy P, Lemma A, Target M. Depression. In: Bateman A, Fonagy P, editors. Handbook of Mentalizing in mental health practice. Washington, DC: American Psychiatric Association; 2012. p. 385–417.
7. Sperber D, Clément F, Heintz C, Mascaro O, Mercier H, Origgi G, et al. Epistemic vigilance. Mind Lang. 2010;25:359–93.

8. Zuroff DC, Kelly AC, Leybman MJ, Blatt SJ, Wampold BE. Between-therapist and within-therapist differences in the quality of the therapeutic relationship: effects on maladjustment and self-critical perfectionism. J Clin Psychol. 2010;66(7):681–97. doi:10.1002/jclp.20683.
9. Fonagy P, Luyten P, Allison E. Teaching to learn from experience: epistemic mistrust, personality, and psychotherapy. Manuscript submitted for publication. 2014.
10. Fonagy P, Edgcumbe R, Moran GS, Kennedy H, Target M. The roles of mental representations and mental processes in therapeutic action. Psychoanal Study Child. 1993;48:9–48.
11. Luyten P, Blatt SJ, Fonagy P. Impairments in self structures in depression and suicide in psychodynamic and cognitive behavioral approaches: implications for clinical practice and research. Int J Cogn Ther. 2013;6(3):265–79. doi:10.1521/ijct.2013.6.3.265.
12. Alonso J, Angermeyer MC, Bernert S, Bruffaerts R, Brugha TS, Bryson H, et al. Prevalence of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. Acta Psychiatr Scand. 2004;109(s420):21–7.
13. Blazer D, Kessler R, McGonagle K, Swartz M. The prevalence and distribution of major depression in a national community sample: the National Comorbidity Survey. Am J Psychiatry. 1994;151(7):979–86.
14. Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA. 2003;289(23):3095–105. doi:10.1001/jama.289.23.3095.
15. Murray CJL, Lopez AD. The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries and risk factors in 1990 and projected to 2020. Cambridge: Harvard University Press; 1996.
16. Segal ZV, Pearson JL, Thase ME. Challenges in preventing relapse in major depression. Report of a National Institute of Mental Health Workshop on state of the science of relapse prevention in major depression. J Affect Disord. 2003;77(2):97–108.
17. Kupfer DJ, Frank E. The interaction of drug- and psychotherapy in the long-term treatment of depression. J Affect Disord. 2001;62(1–2):131–7.
18. Judd LL. The clinical course of unipolar major depressive disorders. Arch Gen Psychiatry. 1997;54(11):989–91. doi:10.1001/archpsyc.1997.01830230015002.
19. Gibb BE, Uhrlass DJ, Grassia M, Benas JS, McGeary J. Children's inferential styles, 5-HTTLPR genotype, and maternal expressed emotion-criticism: an integrated model for the intergenerational transmission of depression. J Abnorm Psychol. 2009;118(4):734–45. doi:10.1037/a0016765.
20. Alloy LB, Abramson LY, Smith JM, Gibb BE, Neeren AM. Role of parenting and maltreatment histories in unipolar and bipolar mood disorders: mediation by cognitive vulnerability to depression. Clin Child Fam Psychol Rev. 2006;9(1):23–64. doi:10.1007/s10567-006-0002-4.
21. Cuijpers P, van Straten A, Bohlmeijer E, Hollon SD, Andersson G. The effects of psychotherapy for adult depression are overestimated: a meta-analysis of study quality and effect size. Psychol Med. 2010;40(2):211–23. doi:10.1017/S0033291709006114.
22. Luyten P, Blatt SJ, Van Houdenhove B, Corveleyn J. Depression research and treatment: are we skating to where the puck is going to be? Clin Psychol Rev. 2006;26(8):985–99. doi:10.1016/j.cpr.2005.12.003.
23. Luyten P, Blatt SJ. Looking back towards the future: is it time to change the DSM approach to psychiatric disorders? The case of depression. Psychiatry. 2007;70(2):85–99. doi:10.1521/psyc.2007.70.2.85.
24. Driessen E, Van HL, Don FJ, Peen J, Kool S, Westra D, et al. The efficacy of cognitive-behavioral therapy and psychodynamic therapy in the outpatient treatment of major depression: a randomized clinical trial. Am J Psychiatry. 2013;170(9):1041–50. doi:10.1176/appi.ajp.2013.12070899.
25. Kool S, Dekker J, Duijsens IJ, de Jonghe F, Puite B. Efficacy of combined therapy and pharmacotherapy for depressed patients with or without personality disorders. Harv Rev Psychiatry. 2003;11(3):133–41.
26. Zanarini MC, Reichman CA, Frankenburg FR, Reich DB, Fitzmaurice G. The course of eating disorders in patients with borderline personality disorder: a 10-year follow-up study. Int J Eat Disord. 2009. doi:10.1002/eat.20689.

27. Zanarini MC, Barison LK, Frankenburg FR, Reich DB, Hudson JI. Family history study of the familial coaggregation of borderline personality disorder with axis I and nonborderline dramatic cluster axis II disorders. J Pers Disord. 2009;23(4):357–69. doi:10.1521/pedi.2009.23.4.357.
28. Grilo CM, Sanislow CA, Shea MT, Skodol AE, Stout RL, Gunderson JG, et al. Two-year prospective naturalistic study of remission from major depressive disorder as a function of personality disorder comorbidity. J Consult Clin Psychol. 2005;73(1):78–85. doi:10.1037/0022-006X.73.1.78.
29. Hilsenroth MJ, Defife JA, Blake MM, Cromer TD. The effects of borderline pathology on short-term psychodynamic psychotherapy for depression. Psychother Res. 2007;17(2):175–88. doi:10.1080/10503300600786748.
30. Mulder RT. Personality pathology and treatment outcome in major depression: a review. Am J Psychiatry. 2002;159(3):359–71.
31. Westen D, Novotny CM, Thompson-Brenner H. The empirical status of empirically supported psychotherapies: assumptions, findings, and reporting in controlled clinical trials. Psychol Bull. 2004;130(4):631–63. doi:10.1037/0033-2909.130.4.631.
32. Fonagy P, Bateman A. Progress in the treatment of borderline personality disorder. Br J Psychiatry. 2006;188:1–3. doi:10.1192/bjp.bp.105.012088.
33. Akiskal HS. Borderline: a adjective still in search of a noun. In: Silver D, Rosenbluth M, editors. Handbook of borderline disorders. Madison: International Universities Press; 1992.
34. Kernberg OF, Caligor E. A psychoanalytic theory of personality disorders. In: Lenzenweger MF, Clarkin JF, editors. Major theories of personality disorder. 2nd ed. New York: Guilford Press; 2005. p. 114–56.
35. Bradley R, Westen D. The psychodynamics of borderline personality disorder: a view from developmental psychopathology. Dev Psychopathol. 2005;17(4):927–57.
36. Skodol AE, Gunderson JG, Pfohl B, Widiger TA, Livesley WJ, Siever LJ. The borderline diagnosis I: psychopathology, comorbidity, and personality structure. Biol Psychiatry. 2002;51(12):936–50. doi:10.1016/S0006-3223(02)01324-0.
37. Skodol AE, Siever LJ, Livesley WJ, Gunderson JG, Pfohl B, Widiger TA. The borderline diagnosis II: biology, genetics, and clinical course. Biol Psychiatry. 2002;51(12):951–63. doi:10.1016/S0006-3223(02)01325-2.
38. Akiskal HS. Demystifying borderline personality: critique of the concept and unorthodox reflections on its natural kinship with the bipolar spectrum. Acta Psychiatr Scand. 2004;110(6):401–7.
39. Linehan MM. Cognitive-behavioral treatment of borderline personality disorder. New York: Guilford Press; 1993.
40. Barnow S, Arens EA, Sieswerda S, Dinu-Biringer R, Spitzer C, Lang S. Borderline personality disorder and psychosis: a review. Curr Psychiatry Rep. 2010;12(3):186–95. doi:10.1007/s11920-010-0107-9.
41. Heim C, Newport DJ, Mletzko T, Miller AH, Hemeroff CB. The link between childhood trauma and depression: insights from HPA axis studies in humans. Psychoneuroendocrinology. 2008;33(6):693–710. doi:10.1016/j.psyneuen.2008.03.008.
42. Blatt SJ, Luyten P. Reactivating the psychodynamic approach to classify psychopathology. In: Millon T, Krueger RF, Simonsen E, editors. Contemporary directions in psychopathology. Scientific foundations of the DSM-V and ICD-11. New York: Guilford Press; 2010. p. 483–514.
43. Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. Am J Psychiatry. 2010;167(7):748–51. doi:10.1176/appi.ajp.2010.09091379.
44. Luyten P, Blatt SJ. Psychodynamic treatment of depression. Psychiatr Clin North Am. 2012;35(1):111–29. doi:10.1016/j.psc.2012.01.001.
45. Fonagy P, Bateman A. The development of borderline personality disorder–a mentalizing model. J Pers Disord. 2008;22(1):4–21. doi:10.1521/pedi.2008.22.1.4.
46. Fonagy P, Luyten P, Bateman A, Gergely G, Strathearn L, Target M, et al. Attachment and personality pathology. In: Clarkin JF, Fonagy P, Gabbard GO, editors. Psychodynamic

psychotherapy for personality disorders. A clinical handbook. Washington, DC: American Psychiatric Publishing; 2010. p. 37–87.
47. Ryan RM, Deci EL. On assimilating identities to the self: a self-determination theory perspective on internalization and integrity within cultures. In: Leary MR, Tangney JP, editors. Handbook of self and identity. New York: Guilford Press; 2003. p. 253–72.
48. Fonagy P, Target M. Attachment and reflective function: their role in self-organization. Dev Psychopathol. 1997;9(4):679–700.
49. Fonagy P, Luyten P. A developmental, mentalization-based approach to the understanding and treatment of borderline personality disorder. Dev Psychopathol. 2009;21(4):1355–81. doi:10.1017/s0954579409990198.
50. Belsky DW, Caspi A, Arseneault L, Bleidorn W, Fonagy P, Goodman M, et al. Etiological features of borderline personality related characteristics in a birth cohort of 12-year-old children. Dev Psychopathol. 2012;24(1):251–65. doi:10.1017/S0954579411000812.
51. Fearon P, Shmueli-Goetz Y, Viding E, Fonagy P, Plomin R. Genetic and environmental influences on adolescent attachment. J Child Psychol Psychiatry. 2013. doi:10.1111/jcpp.12171.
52. Luyten P, Mayes LC, Fonagy P, van Houdenhove B. The interpersonal regulation of stress: a developmental framework. Manuscript submitted for publication. 2014.
53. Drevets WC, Price JL, Furey ML. Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. Brain Struct Funct. 2008;213(1–2):93–118. doi:10.1007/s00429-008-0189-x.
54. Johnson MK, Nolen-Hoeksema S, Mitchell KJ, Levin Y. Medial cortex activity, self-reflection and depression. Soc Cogn Affect Neurosci. 2009;4(4):313–27. doi:10.1093/scan/nsp022.
55. Savitz J, Drevets WC. Bipolar and major depressive disorder: neuroimaging the developmental-degenerative divide. Neurosci Biobehav Rev. 2009;33(5):699–771. doi:10.1016/j.neubiorev.2009.01.004.
56. Blatt SJ. Experiences of depression: theoretical, clinical and research perspectives. Washington, DC: American Psychological Association; 2004.
57. Panksepp J, Watt D. Why does depression hurt? Ancestral primary-process separation-distress (PANIC/GRIEF) and diminished brain reward (SEEKING) processes in the genesis of depressive affect. Psychiatry. 2011;74(1):5–13. doi:10.1521/psyc.2011.74.1.5.
58. Blatt SJ, Luyten P. Depression as an evolutionary conserved mechanism to terminate separation-distress: only part of the biopsychosocial story? [Commentary on Watt & Panksepp]. Neuropsychoanalysis. 2009;11:52–61.
59. Gunderson JG. Disturbed relationships as a phenotype for borderline personality disorder. Am J Psychiatry. 2007;164(11):1637–40. doi:10.1176/appi.ajp.2007.07071125.
60. Blatt SJ, Auerbach JS. Differential cognitive disturbances in three types of borderline patients. J Pers Disord. 1988;2:198–211.
61. Northoff G, Heinzel A, de Greck M, Bermpohl F, Dobrowolny H, Panksepp J. Self-referential processing in our brain–a meta-analysis of imaging studies on the self. Neuroimage. 2006; 31(1):440–57.
62. Mennin DS, Fresco DM. What, me worry and ruminate about DSM-5 and RDoC? The importance of targeting negative self-referential processing. Clin Psychol Sci Pract. 2013; 20(3):258–67. doi:10.1111/cpsp.12038.
63. Lemma A, Target M, Fonagy P. The development of a brief psychodynamic intervention (dynamic interpersonal therapy) and its application to depression: a pilot study. Psychiatry. 2011;74(1):41–8. doi:10.1521/psyc.2011.74.1.41.
64. Lee A, Hankin BL. Insecure attachment, dysfunctional attitudes, and low self-esteem predicting prospective symptoms of depression and anxiety during adolescence. J Clin Child Adolesc Psychol. 2009;38(2):219–31. doi:10.1080/15374410802698396.
65. Grunebaum MF, Galfalvy HC, Mortenson LY, Burke AK, Oquendo MA, Mann JJ. Attachment and social adjustment: relationships to suicide attempt and major depressive episode in a prospective study. J Affect Disord. 2010;123(1–3):123–30. doi:10.1016/j.jad.2009.09.010.
66. Blatt SJ, Luyten P. A structural-developmental psychodynamic approach to psychopathology: two polarities of experience across the life span. Dev Psychopathol. 2009;21(3):793–814.

67. Blatt SJ, Homann E. Parent-child interaction in the etiology of dependent and self-critical depression. Clin Psychol Rev. 1992;12(1):47–91. doi:10.1016/0272-7358(92)90091-L.
68. Russell JJ, Moskowitz DS, Zuroff DC, Sookman D, Paris J. Stability and variability of affective experience and interpersonal behavior in borderline personality disorder. J Abnorm Psychol. 2007;116(3):578–88. doi:10.1037/0021-843X.116.3.578.
69. Kopala-Sibley DC, Zuroff DC, Russell JJ, Moskowitz DS, Paris J. Understanding heterogeneity in borderline personality disorder: differences in affective reactivity explained by the traits of dependency and self-criticism. J Abnorm Psychol. 2012;121(3):680–91. doi:10.1037/a0028513.
70. Conradi HJ, de Jonge P. Recurrent depression and the role of adult attachment: a prospective and a retrospective study. J Affect Disord. 2009;116(1–2):93–9. doi:10.1016/j.jad.2008.10.027.
71. Pietrek C, Elbert T, Weierstall R, Muller O, Rockstroh B. Childhood adversities in relation to psychiatric disorders. Psychiatry Res. 2013;206(1):103–10. doi:10.1016/j.psychres.2012.11.003.
72. Lupien SJ, McEwen BS, Gunnar MR, Heim C. Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nat Rev Neurosci. 2009;10(6):434–45.
73. Champagne FA, Curley JP. Epigenetic mechanisms mediating the long-term effects of maternal care on development. Neurosci Biobehav Rev. 2009;33(4):593–600. doi:10.1016/j.neubiorev.2007.10.009.
74. Gunnar M, Quevedo K. The neurobiology of stress and development. Annu Rev Psychol. 2007;58(1):145–73. doi:10.1146/annurev.psych.58.110405.085605.
75. DeVries AC, Craft TK, Glasper ER, Neigh GN, Alexander JK. Social influences on stress responses and health. Psychoneuroendocrinology. 2007;32(6):587–603. doi:10.1016/j.psyneuen.2007.04.007.
76. Neumann ID. Brain oxytocin: a key regulator of emotional and social behaviours in both females and males. J Neuroendocrinol. 2008;20(6):858–65. doi:10.1111/j.1365-2826.2008.01726.x.
77. Bakermans-Kranenburg MJ, Van Ijzendoorn MH, Mesman J, Alink LR, Juffer F. Effects of an attachment-based intervention on daily cortisol moderated by dopamine receptor D4: a randomized control trial on 1- to 3-year-olds screened for externalizing behavior. Dev Psychopathol. 2008;20(3):805–20. doi:10.1017/S0954579408000382.
78. Wichers M, Geschwind N, Jacobs N, Kenis G, Peeters F, Derom C, et al. Transition from stress sensitivity to a depressive state: longitudinal twin study. Br J Psychiatry. 2009;195(6):498–503. doi:10.1192/bjp.bp.108.056853.
79. Bifulco A, Kwon J, Jacobs C, Moran PM, Bunn A, Beer N. Adult attachment style as mediator between childhood neglect/abuse and adult depression and anxiety. Soc Psychiatry Psychiatr Epidemiol. 2006;41(10):796–805. doi:10.1007/s00127-006-0101-z.
80. Styron T, Janoff-Bulman R. Childhood attachment and abuse: long-term effects on adult attachment, depression, and conflict resolution. Child Abuse Negl. 1997;21(10):1015–23.
81. Crowell SE, Beauchaine TP, Linehan MM. A biosocial developmental model of borderline personality: elaborating and extending Linehan's theory. Psychol Bull. 2009;135(3):495–510. doi:10.1037/a0015616.
82. Risch N, Herrell R, Lehner T, Liang KY, Eaves L, Hoh J, et al. Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: a meta-analysis. JAMA. 2009;301(23):2462–71. doi:10.1001/jama.2009.878.
83. Calati R, Gressier F, Balestri M, Serretti A. Genetic modulation of borderline personality disorder: systematic review and meta-analysis. J Psychiatr Res. 2013;47(10):1275–87. doi:10.1016/j.jpsychires.2013.06.002.
84. Carter CS, Grippo AJ, Pournajafi-Nazarloo H, Ruscio MG, Porges SW. Oxytocin, vasopressin and sociality. Prog Brain Res. 2008;170:331–6. doi:10.1016/S0079-6123(08)00427-5.
85. Heinrichs M, Domes G. Neuropeptides and social behaviour: effects of oxytocin and vasopressin in humans. Prog Brain Res. 2008;170:337–50. doi:10.1016/S0079-6123(08)00428-7.
86. Gordon I, Zagoory-Sharon O, Schneiderman I, Leckman JF, Weller A, Feldman R. Oxytocin and cortisol in romantically unattached young adults: associations with bonding and psychological distress. Psychophysiology. 2008;45(3):349–52. doi:10.1111/j.1469-8986.2008.00649.x.

87. Insel TR, Young LJ. The neurobiology of attachment. Nat Rev Neurosci. 2001;2(2):129–36. doi:10.1038/35053579.
88. Feldman R, Weller A, Zagoory-Sharon O, Levine A. Evidence for a neuroendocrinological foundation of human affiliation: plasma oxytocin levels across pregnancy and the postpartum period predict mother-infant bonding. Psychol Sci. 2007;18(11):965–70. doi:10.1111/j.1467-9280.2007.02010.x.
89. Levine A, Zagoory-Sharon O, Feldman R, Weller A. Oxytocin during pregnancy and early postpartum: individual patterns and maternal-fetal attachment. Peptides. 2007;28(6):1162–9. doi:10.1016/j.peptides.2007.04.016.
90. Fries E, Hesse J, Hellhammer J, Hellhammer DH. A new view on hypocortisolism. Psychoneuroendocrinology. 2005;30(10):1010–6. doi:10.1016/j.psyneuen.2005.04.006.
91. Meinlschmidt G, Heim C. Sensitivity to intranasal oxytocin in adult men with early parental separation. Biol Psychiatry. 2007;61(9):1109–11. doi:10.1016/j.biopsych.2006.09.007.
92. Costa B, Pini S, Gabelloni P, Abelli M, Lari L, Cardini A, et al. Oxytocin receptor polymorphisms and adult attachment style in patients with depression. Psychoneuroendocrinology. 2009;34(10):1506–14. doi:10.1016/j.psyneuen.2009.05.006.
93. Cyranowski JM, Hofkens TL, Frank E, Seltman H, Cai HM, Amico JA. Evidence of dysregulated peripheral oxytocin release among depressed women. Psychosom Med. 2008;70(9):967–75. doi:10.1097/Psy.0b013e318188ade4.
94. Gotlib IH, Hamilton JP, Cooney RE, Singh MK, Henry ML, Joormann J. Neural processing of reward and loss in girls at risk for major depression. Arch Gen Psychiatry. 2010;67(4):380–7. doi:10.1001/archgenpsychiatry.2010.13.
95. Bertsch K, Schmidinger I, Neumann ID, Herpertz SC. Reduced plasma oxytocin levels in female patients with borderline personality disorder. Horm Behav. 2013;63(3):424–9. doi:10.1016/j.yhbeh.2012.11.013.
96. Bartz J, Simeon D, Hamilton H, Kim S, Crystal S, Braun A, et al. Oxytocin can hinder trust and cooperation in borderline personality disorder. Soc Cogn Affect Neurosci. 2011;6(5):556–63. doi:10.1093/Scan/Nsq085.
97. Stanley B, Siever LJ. The interpersonal dimension of borderline personality disorder: toward a neuropeptide model. Am J Psychiatry. 2010;167(1):24–39. doi:10.1176/appi.ajp.2009.09050744.
98. Luyten P, Fonagy P. Probing the interpersonal phenotype of borderline personality disorder: an attachment and mentalizing perspective. Manuscript submitted for publication. 2014.
99. Silk KR. The quality of depression in borderline personality disorder and the diagnostic process. J Pers Disord. 2010;24(1):25–37. doi:10.1521/pedi.2010.24.1.25.
100. Zanarini MC, Frankenburg FR, DeLuca CJ, Hennen J, Khera GS, Gunderson JG. The pain of being borderline: dysphoric states specific to borderline personality disorder. Harv Rev Psychiatry. 1998;6(4):201–7.
101. Southwick SM, Yehuda R, Giller EL. Psychological dimensions of depression in borderline personality disorder. Am J Psychiatry. 1995;152(5):789–91.
102. Rogers JH, Widiger TA, Krupp A. Aspects of depression associated with borderline personality disorder. Am J Psychiatry. 1995;152(2):268–70.
103. Wixom J, Ludolph P, Westen D. The quality of depression in adolescents with borderline personality disorder. J Am Acad Child Adolesc Psychiatry. 1993;32(6):1172–7. doi:10.1097/00004583-199311000-00009.
104. Gratz KL, Breetz A, Tull MT. The moderating role of borderline personality in the relationships between deliberate self-harm and emotion-related factors. Personal Ment Health. 2010;4(2):96–107. doi:10.1002/Pmh.102.
105. Hawes DJ, Helyer R, Herlianto EC, Willing J. Borderline personality features and implicit shame-prone self-concept in middle childhood and early adolescence. J Clin Child Adolesc Psychol. 2013;42(3):302–8. doi:10.1080/15374416.2012.723264.
106. Leichsenring F. Quality of depressive experiences in borderline personality disorders: differences between patients with borderline personality disorder and patients with higher levels of personality organization. Bull Menninger Clin. 2004;68(1):9–22.

107. Fonagy P, Gergely G, Jurist E, Target M. Affect regulation, mentalization and the development of the self. New York: Other Press; 2002.
108. Aviram RB, Brodsky BS, Stanley B. Borderline personality disorder, stigma, and treatment implications. Harv Rev Psychiatry. 2006;14(5):249–56. doi:10.1080/10673220600975121.
109. Bateman AW. Thick- and thin-skinned organisations and enactment in borderline and narcissistic disorders. Int J Psychoanal. 1998;79(Pt 1):13–25.
110. Gabbard GO. Technical approaches to transference hate in the analysis of borderline patients. Int J Psychoanal. 1991;72(Pt 4):625–37.
111. Yeh Z-T, Liu S-I. Depressive realism: evidence from false interpersonal perception. Psychiatry Clin Neurosci. 2007;61(2):135–41.
112. Moore MT, Fresco DM. Depressive realism and attributional style: implications for individuals at risk for depression. Behav Ther. 2007;38(2):144–54.
113. Domes G, Czieschnek D, Weidler F, Berger C, Fast K, Herpertz SC. Recognition of facial affect in borderline personality disorder. J Pers Disord. 2008;22(2):135–47. doi:10.1521/pedi.2008.22.2.135.
114. Lynch TR, Rosenthal MZ, Kosson DS, Cheavens JS, Lejuez CW, Blair RJ. Heightened sensitivity to facial expressions of emotion in borderline personality disorder. Emotion. 2006;6(4):647–55. doi:10.1037/1528-3542.6.4.647.
115. Schulze L, Domes G, Koppen D, Herpertz SC. Enhanced detection of emotional facial expressions in borderline personality disorder. Psychopathology. 2013;46(4):217–24. doi:10.1159/000341730.
116. Fonagy P, Leigh T, Steele M, Steele H, Kennedy R, Mattoon G, et al. The relation of attachment status, psychiatric classification, and response to psychotherapy. J Consult Clin Psychol. 1996;64(1):22–31.
117. Fischer-Kern M, Schuster P, Kapusta ND, Tmej A, Buchheim A, Rentrop M, et al. The relationship between personality organization, reflective functioning, and psychiatric classification in borderline personality disorder. Psychoanal Psychol. 2010;27(4):395–409. doi:10.1037/a0020862.
118. Gullestad FS, Johansen MS, Hoglend P, Karterud S, Wilberg T. Mentalization as a moderator of treatment effects: findings from a randomized clinical trial for personality disorders. Psychother Res. 2012. doi:10.1080/10503307.2012.684103.
119. Levy KN, Meehan KB, Kelly KM, Reynoso JS, Weber M, Clarkin JF, et al. Change in attachment patterns and reflective function in a randomized control trial of transference-focused psychotherapy for borderline personality disorder. J Consult Clin Psychol. 2006;74(6):1027–40. doi:10.1037/0022-006X.74.6.1027.
120. Preissler S, Dziobek I, Ritter K, Heekeren HR, Roepke S. Social cognition in borderline personality disorder: evidence for disturbed recognition of the emotions, thoughts, and intentions of others. Front Behav Neurosci. 2010;4:182. doi:10.3389/fnbeh.2010.00182.
121. Ritter K, Dziobek I, Preissler S, Ruter A, Vater A, Fydrich T, et al. Lack of empathy in patients with narcissistic personality disorder. Psychiatry Res. 2011;187(1–2):241–7. doi:10.1016/j.psychres.2010.09.013.
122. Sharp C, Pane H, Ha C, Venta A, Patel AB, Sturek J, et al. Theory of mind and emotion regulation difficulties in adolescents with borderline traits. J Am Acad Child Adolesc Psychiatry. 2011;50(6):563–73. doi:10.1016/j.jaac.2011.01.017.
123. Bolton JM, Pagura J, Enns MW, Grant B, Sareen J. A population-based longitudinal study of risk factors for suicide attempts in major depressive disorder. J Psychiatr Res. 2010;44(13):817–26. doi:10.1016/j.jpsychires.2010.01.003.
124. Sharp C, Green KL, Yaroslavsky I, Venta A, Zanarini MC, Pettit J. The incremental validity of borderline personality disorder relative to major depressive disorder for suicidal ideation and deliberate self-harm in adolescents. J Pers Disord. 2012;26(6):927–38. doi:10.1521/pedi.2012.26.6.927.
125. Luyten P, Fonagy P, Lowyck B, Vermote R. Assessment of mentalization. In: Bateman AW, Fonagy P, editors. Handbook of mentalizing in mental health practice. Washington, DC: American Psychiatric Publishing; 2012. p. 43–66.

126. Sharp C, Ha C, Carbone C, Kim S, Perry K, Williams L, et al. Hypermentalizing in adolescent inpatients: treatment effects and association with borderline traits. J Pers Disord. 2013; 27(1):3–18.
127. Tyrer P, Tom B, Byford S, Schmidt U, Jones V, Davidson K, et al. Differential effects of manual assisted cognitive behavior therapy in the treatment of recurrent deliberate self-harm and personality disturbance: the POPMACT study. J Pers Disord. 2004;18(1):102–16.
128. Barth J, Munder T, Gerger H, Nuesch E, Trelle S, Znoj H, et al. Comparative efficacy of seven psychotherapeutic interventions for patients with depression: a network meta-analysis. PLoS Med. 2013;10(5):e1001454. doi:10.1371/journal.pmed.1001454.
129. Levy KN, Beeney JE, Wasserman RH, Clarkin JF. Conflict begets conflict: executive control, mental state vacillations, and the therapeutic alliance in treatment of borderline personality disorder. Psychother Res. 2010;20(4):413–22. doi:10.1080/10503301003636696.
130. Cash SK, Hardy GE, Kellett S, Parry G. Alliance ruptures and resolution during cognitive behaviour therapy with patients with borderline personality disorder. Psychother Res. 2014;24:132–45.
131. Bateman A, Fonagy P. Mentalization based treatment for borderline personality disorder. World Psychiatry. 2010;9(1):11–5.
132. Main M. Metacognitive knowledge, metacognitive monitoring, and singular (coherent) vs. multiple (incoherent) model of attachment. In: Parkes C, Stevenson-Hinde J, Marris P, editors. Attachment across the life circle. London: Routledge; 1991. p. 127–59.
133. Chisolm K. A three year follow-up of attachment and indiscriminate friendliness in children adopted from Russian orphanages. Child Dev. 1998;69:1092–106.
134. Owen MT, Cox MJ. Marital conflict and the development of infant-parent attachment relationships. J Fam Psychol. 1997;11:152–64.
135. Carlson V, Cicchetti D, Barnett D, Braunwald K. Disorganised/disoriented attachment relationships in maltreated infants. Dev Psychol. 1989;25:525–31.
136. Main M, Solomon J. Procedures for identifying infants as disorganized/disorientated during the Ainsworth strange situation. In: Greenberg M, Cicchetti D, Cummings E, editors. Attachment during the Preschool years: theory, research and interventions. Chicago: Chicago University Press; 1990. p. 121–60.
137. Lyons-Ruth K. Contributions of the mother-infant relationship to dissociative, borderline, and conduct symptoms in young adulthood. Infant Ment Health J. 2008;29(3):203–18. doi:10.1002/imhj.20173.
138. Crawford TN, Cohen PR, Chen H, Anglin DM, Ehrensaft M. Early maternal separation and the trajectory of borderline personality disorder symptoms. Dev Psychopathol. 2009;21(3): 1013–30.
139. Choi-Kain LW, Fitzmaurice GM, Zanarini MC, Laverdiere O, Gunderson JG. The relationship between self-reported attachment styles, interpersonal dysfunction, and borderline personality disorder. J Nerv Ment Dis. 2009;197(11):816–21. doi:10.1097/NMD.0b013e3181bea56e.
140. Bifulco A, Moran PM, Ball C, Bernazzani O. Adult attachment style. I: its relationship to clinical depression. Soc Psychiatry Psychiatr Epidemiol. 2002;37:50–9.
141. Bifulco A, Moran PM, Ball C, Lillie A. Adult attachment style. II: its relationship to psychosocial depressive-vulnerability. Soc Psychiatry Psychiatr Epidemiol. 2002;37:60–7.
142. Fonagy P. An attachment theory approach to treatment of the difficult patient. Bull Menninger Clin. 1998;62(2):147–69.
143. Main M. The organized categories of infant, child, and adult attachment: flexible vs. inflexible attention under attachment-related stress. J Am Psychoanal Assoc. 2000;48(4):1055–96.
144. Westen D, Shedler J, Bradley B, DeFife JA. An empirically derived taxonomy for personality diagnosis: bridging science and practice in conceptualizing personality. Am J Psychiatry. 2012;169(3):273–84. doi:10.1176/appi.ajp.2011.11020274.
145. Sperber D, Wilson DB. Relevance and meaning. Cambridge: Cambridge University Press; 2012.
146. Corriveau KH, Harris PL, Meins E, Fernyhough C, Arnott B, Elliott L, et al. Young children's trust in their mother's claims: longitudinal links with attachment security in infancy. Child Dev. 2009;80(3):750–61. doi:10.1111/j.1467-8624.2009.01295.x.

147. Segal ZV, Williams JMG, Teasdale JD. Mindfulness-based cognitive therapy for depression. 2nd ed. New York: Guilford Press; 2013.
148. Watkins E, Teasdale JD. Adaptive and maladaptive self-focus in depression. J Affect Disord. 2004;82(1):1–8.
149. Lemma A, Target M, Fonagy P. The development of a brief psychodynamic protocol for depression: dynamic interpersonal therapy (DIT). Psychoanal Psychother. 2010;24(4): 329–46.
150. Hoglend P. Analys of transference in psychodynamic psychotherapy. Can J Psychoanal. 2004;12:279–300.
151. Hoglend P, Amlo S, Marble A, Bogwald KP, Sorbye O, Sjaastad MC, et al. Analysis of the patient-therapist relationship in dynamic psychotherapy: an experimental study of transference interpretations. Am J Psychiatry. 2006;163(10):1739–46.
152. Hoglend P, Bogwald K-P, Amlo S, Marble A, Ulberg R, Sjaastad MC, et al. Transference interpretations in dynamic psychotherapy: do they really yield sustained effects? Am J Psychiatry. 2008;165(6):763–71. doi:10.1176/appi.ajp.2008.07061028.
153. Johansson P, Hoglend P, Ulberg R, Bogwald KP, Amlo S, Marble A, et al. The mediating role of insight for long-term improvements in psychodynamic therapy. J Consult Clin Psychol. 2010;78(3):438–48.
154. McCullough L, Winston A, Farber BA, Porter F, Pollack J, Laikin M, et al. The relationship of patient-therapist interaction to outcome in brief psychotherapy. Psychotherapy. 1991;28: 525–33.
155. Kernberg OF. Internal world and external reality: object relations theory applied. New York: Jason Aronson; 1980.
156. Driessen E, Cuijpers P, de Maat SCM, Abbass AA, de Jonghe F, Dekker JJM. The efficacy of short-term psychodynamic psychotherapy for depression: a meta-analysis. Clin Psychol Rev. 2010;30(1):25–36.
157. Abbass A, Town J, Driessen E. The efficacy of short-term psychodynamic psychotherapy for depressive disorders with comorbid personality disorder. Psychiatry. 2011;74(1):58–71.
158. Town JM, Abbass A, Hardy G. Short-term psychodynamic psychotherapy for personality disorders: a critical review of randomized controlled trials. J Pers Disord. 2011; 25(6):723–40.
159. Leichsenring F, Abbass A, Luyten P, Hilsenroth M, Rabung S. The emerging evidence for long-term psychodynamic therapy. Psychodyn Psychiatry. 2013;41(3):361–84. doi:10.1521/pdps.2013.41.3.361.
160. Leichsenring F, Rabung S. Long-term psychodynamic psychotherapy in complex mental disorders: update of a meta-analysis. Br J Psychiatry. 2011;199(1):15–22. doi:10.1192/bjp.bp.110.082776.
161. Bateman A, Fonagy P. 8-year follow-up of patients treated for borderline personality disorder: mentalization-based treatment versus treatment as usual. Am J Psychiatry. 2008;165(5): 631–8. doi:10.1176/appi.ajp.2007.07040636.
162. Rossouw TI, Fonagy P. Mentalization-based treatment for self-harm in adolescents: a randomized controlled trial. J Am Acad Child Adolesc Psychiatry. 2012;51(12):1304–13.e3. doi:10.1016/j.jaac.2012.09.018.

Part VI
Discussion

Chapter 14
Conclusion: Integration and Synthesis

Lois W. Choi-Kain and John G. Gunderson

The relationship between mood disorders and borderline personality disorder (BPD) has long been controversial, fueling fierce debates about psychiatric diagnosis and treatment [1–3]. This controversy has spurred the development of a significant body of research, which allows us to ground our hypotheses and claims primarily in evidence rather than polemics. This book is an effort to review, synthesize, and evaluate the current evidence on the relationship between mood and borderline personality disorders. We hope to promote more objective and tentative conclusions that inform more effective clinical care of and continued research on the interaction between these commonly encountered disorders.

The adversarial nature of the original debates between the mood and personality disorder worlds arose from territorial agendas, revolving around efforts to establish the legitimacy of these respective disorders in an era where the criteria for most psychiatric diagnoses known today were in early stages of empirical validation. In the context of these diagnostic turf wars, much of the language and tone of the debate between mood and personality disorder experts was competitive and undercutting. The chapters contributed by Paris as well as Ghaemi and Barroilhet represent the evolution of this debate. Paris argues that the trend towards biological reductionism has caused neurobiological understandings and psychopharmacologic treatments to edge out psychoanalytic concepts and psychotherapeutic interventions.

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This shift has pushed mental health clinicians to prefer simpler conceptualizations of psychiatric presentations in terms of mood disorders as opposed to more complex formulations in terms of personality disorders. Ghaemi and Barroilhet make a similar distinction with different implications. They argue that bipolar disorder is more of an illness or disease than BPD because it is almost completely genetic in etiology. Both Paris and Ghaemi and Barroilhet distinguish BPD as a complex clinical picture which develops primarily from psychosocial influences. Both chapters focus their criticism more at the way in which the diagnostic concepts are applied and less at the legitimacy of mood or borderline diagnoses. At the same time, these chapters still embody dichotomizing tendencies that falsely or simplistically separate biologically and psychosocially based disorders and interventions. This dichotomy provides clinicians and researchers with hard edges around which to draw lines between categories of psychiatric illness, providing clarity in the face of clinical complexity. The problem arises when these dichotomizing tendencies position disorders as competitive, suggesting, as Ghaemi and Barroilhet indicate, that the overlap between psychiatric syndromes simply means one represents the other.

This collection of chapters reviews and synthesizes the existing literature to enable mental health professionals to develop a more nuanced and realistic way of interpreting and managing the overlaps and differences between these disorders. While residue of this historic hostility still exists, the current conversation between the mood and personality disorder camps accommodates both recognition that (1) unipolar depression, bipolar disorder, and BPD are valid diagnostic constructs and (2) when considered as part of a mutually exclusive differential diagnosis, the use of these diagnostic categories tends to oversimplify the relationships between the underlying vulnerabilities, phenotypic features, and indicated treatments for patients presenting with complex comorbidity and/or atypical variations of these illnesses. As the chapters by Paris and Ghaemi/Barroilhet suggest, our current use of diagnostic constructs is limited and leads to reductive and simplified clinical management. This tendency contributes to misdiagnosis or ineffective prioritization of one diagnosis over another.

In an attempt to clarify what we now know about the overlaps and distinctions between mood disorders and BPD, the authors in this volume have reviewed the current literature on the clinical and neurobiological profiles, development, and course, as well as psychopharmacologic and psychotherapeutic interventions for these disorders. This review has traced five general conclusions from the current status of knowledge about the relationship between these disorders:

1. Depression and BPD phenotypically diverge yet are highly comorbid, suggesting overlapping underlying liabilities. Depression and BPD also interact significantly in longitudinal course.
2. Bipolar disorder and BPD phenotypically overlap yet are infrequently comorbid, suggesting more disparate etiologies. This leads to increased diagnostic confusion and misdiagnosis.
3. Depression, bipolar disorder, and BPD all involve the interaction between temperamental or trait-like features and acute episodic symptoms or state-like features.

4. Real-world clinical settings involve patients who may present with symptoms, precursors, and risk factors shared among mood disorders and BPD. Premature diagnostic certainty results in therapeutic overkill with overly specialized intensive treatment mismatched to presentations. Clinical interventions scaled with clinical staging considerations may reduce the tendency towards misdiagnosis and iatrogenic interventions.
5. Psychopharmacologic treatment is primary for depression and bipolar disorder and adjunctive for BPD. Psychotherapeutic approaches are primary for BPD and adjunctive for depression and bipolar disorder. A combination of approaches is indicated with comorbid or diagnostically unclear presentations, but further research is needed to determine the effectiveness of combined treatments and step-wise approaches to care.

The remainder of this summary will review and consider the evidence presented in this text supporting each of these conclusions.

Depression and BPD: Superficially Divergent, Fundamentally Overlapping

Depression and BPD are clinically distinct disorders with divergent treatment strategies but appear to stem from shared underlying vulnerabilities. Depression is one of psychiatry's most prevalent disorders with heterogeneous variations that respond to a diversity of treatments. BPD is a specific and severe clinical syndrome, which was distinguished initially, per Choi-Kain and Rodriguez-Villa's historical review, by its lack of or negative response to typical treatments which were generally effective for a range of common mental disorders. A number of chapters (Goodman et al.; Yalch, Hopwood, and Zanarini; Silk) in this book highlight differences in clinical features of MDD and BPD. Silk and Goodman et al. characterize depressive features of individuals with BPD in terms of dysphoria, emptiness, loneliness, and fears of abandonment. In addition, core features of impulsivity and interpersonal sensitivity in BPD distinguish it from MDD. The severity of mood symptoms and degree of functional impairment in individuals with BPD exceeds that found in those with MDD. The limited response of BPD symptoms to antidepressants also suggests a significant clinical difference between MDD and BPD. These differences suggest that these disorders are distinct and not just reflections of each other.

At the same time, comorbidity between MDD and BPD is significant. A vast majority of BPD samples, that is, 70–80 % [4, 5], report comorbidity with MDD. Conversely 50–85 % of outpatients with MDD have personality disorders, of which BPD is the most prevalent [6]. Furthermore, family studies have established a significant risk for MDD in relatives of probands with BPD [7–9]. Although there are clear differences in clinical phenomenology and biological features which can differentiate these two diagnostic entities as noted in Goodman and collaborators' chapter (i.e., brain region involvement, neurohormonal indices, and sleep architecture), the

high rate of co-occurrence and familiality implies the existence of shared underlying liabilities between the two disorders. These underlying liabilities increase the likelihood of not only developing either MDD or BPD but also of developing both disorders comorbidly. In the last decade, research on broader underlying familial internalizing and externalizing dimensions of psychopathology has confirmed overlaps in latent liability factors that explained the co-occurrence of disorders [10–12]. Studies have indicated that BPD is associated with both internalizing and externalizing factors, which explains its complex comorbidity pattern [13, 14].

Skodol summarizes the literature on the longitudinal interactions between MDD and BPD in Chap. 10. His summary illustrates that the co-occurrence of BPD and MDD is associated with both slowed remission and increased relapse in both disorders, thereby contributing to a greater chronicity in each. The reciprocal interactions between the two disorders suggest there may be shared underlying factors that contribute to the persistence and recurrence of acute symptoms in both disorders. Additionally, Yalch, Hopwood, and Zanarini report that as MDD severity increases, its overlap with BPD increases.

While many possible explanations for the interaction between MDD and BPD have been proposed (see chapter by Goodman et al.), the current state of knowledge seems to support the following hypotheses: (1) MDD and BPD are manifestations of the same phenomenon, (2) MDD and BPD share common vulnerabilities, and (3) MDD and BPD share common biological features which foster each other's development [15, 16]. These hypotheses are not mutually exclusive. In order to refine our understanding of the complex relationship between the two disorders, it is necessary to first identify the shared liabilities and biological features.

Throughout this book, several authors have reported on the role of personality traits or temperamental endowments, such as negative affectivity, emotional dysregulation, and interpersonal hypersensitivity in the development of both mood and borderline personality disorders. Goodman et al. describe several biological characteristics including amygdala hyperreactivity, subgenual ACC volume changes, and deficient serotinergic function that are thought to underpin the emotional dysregulation seen in both MDD and BPD. Genetic findings point to serotonin, tryptophan hydroxylase, and monoamine oxidase systems as potential sources of the shared vulnerability towards altered processing of social and emotional information. Future research is needed to clarify the biological factors that may underlie the relationship between emotional and relational characteristics contributing to liability for both disorders.

In both the depression and BPD research literatures, interpersonal factors have been implicated as central vulnerabilities contributing to risk for developing psychopathology in the context of life stress [17–19]. Interpersonal features, such as attachment insecurity and rejection sensitivity, which have distinguished those with BPD from those without, appear to also be associated with MDD but at lesser degrees [20, 21]. Attachment insecurity and rejection sensitivity may be nonspecific features which confer risk to a number of disorders, but may be more severe and prevalent in individuals with BPD. The degree to which these interpersonal factors contribute to risk for BPD and its comorbidity as well as their relevant underlying biological mechanisms requires further study.

Bipolar Disorder and BPD: Superficially Overlapping, Fundamentally Divergent

Several chapters in this text describe the overlap between bipolar and borderline personality disorders as more limited than the overlap between depression and BPD. All authors in this book agree that bipolar disorder and BPD are distinct disorders which both tend to be delayed in diagnosis and thereby delayed in being adequately treated. Impulsivity is a key feature shared by both disorders, but not considered to be at the core of either. Mood fluctuations are also shared by both disorders, but, as explicated in the chapter by Reich, the affective instability seen in BPD involves more shifts between anger, depression, and anxiety, whereas those seen in bipolar disorder involve more euphoria. Ghaemi and Barroilhet assert that a comparison of these disorders is akin to one of red skies and red apples, suggesting a relationship at a superficial level. Their superficial similarities lead to significant underdiagnosis of BPD with overdiagnosis of bipolar disorder as described by Zimmerman and Morgan in their chapter.

Chapters contributed by Ghaemi and Barroilhet as well as Reich outline important clinical and biological differences between BPD and bipolar disorder. Symptoms of dissociation, parasuicidal behavior, and recurrent deliberate self-harm distinguish borderline patients from bipolar patients. Bipolar patients are more likely to describe euphoric mood, increased goal-directed activity, and psychomotor agitation. Reich reports that the affective instability seen in both disorders stems from different neurobiological bases. Ghaemi and Barroilhet also emphasize the high rates of trauma history in BPD, arguing that environmental factors have a more significant effect on the development of BPD, whereas genetics contribute more strongly to the development of bipolar disorder. The low rate of co-occurrence and lack of influence on each other's course longitudinally further supports the notion that these are two distinct, unrelated disorders.

Taken together, the authors contributing to this text suggest that borderline personality and bipolar disorder are distinct and unrelated, but their overlaps in symptoms lead to problems of misdiagnosis rather than co-occurrence. Morgan and Zimmerman as well as Ghaemi and Barroilhet suggest using family history and trauma history as clinical indicators. These clinical features may lean practitioners towards either a bipolar or borderline diagnosis. In reality, when clinicians base their diagnostic impressions on self-report, diagnostic clarity remains at times elusive despite the current understanding of differences between these diagnoses.

A specific area of more murky differentiation exists between bipolar type II and borderline personality disorders. As Skodol proposes in his chapter, the overlaps between these disorders in the realm of interpersonal sensitivity, childhood trauma, and recurrent suicidality combined with the relatively weaker associations with family history of bipolar I and more variable treatment response to mood stabilizers point to the possibility that these two disorders may be more related than bipolar type I and borderline personality. The only longitudinal interaction between

bipolar disorder and BPD is that type II bipolar disorder slows time to remission of BPD. Skodol suggests that the combination of BPD and bipolar type II may represent a more severe variant of BPD. More research is needed to assess the relative relationship of bipolar II to both BPD and bipolar I.

Temperament, Mood, and Personality: Models for Overlapping and Interactive Concepts

In both the mood and personality disorder literatures, researchers have been investigating the relationship between temperamental endowments, personality features, stressful life events (e.g., trauma), and psychopathology. As described by Lara et al., temperament is conceptualized as an innate disposition that influences basic emotional, behavioral, and cognitive responses. Mood is then expressed from a temperamental basis in response to external or internal stimuli. The position of personality in relation to temperament and mood is variable. Personality traits are similar to temperamental characteristics that are enduring and biologically based. However, like mood, personality is expressed in terms of the interface between temperamental characteristics and environmental exposures. Chapters by Lara et al. as well as Yalch, Hopwood, and Zanarini represent the dimensional and categorical approaches developed to assess and explain the relevance of temperament, mood, and personality to etiology and symptomatic manifestations of these illnesses.

A vast number of assessments and models of temperament and personality have been proposed and validated. Lara et al. present a complex framework combining dimensional and categorical models of temperament and personality, organized in a similar way to the proposed (and rejected) revisions to personality disorder diagnosis for the DSM-V. Lara's Affective and Emotional Composite Temperament (AFECTS) model integrates a number of emotional traits (e.g., volition/energy, drive, anger, fear, caution, emotional sensitivity, anxiety, control, coping, and stability) which represent neurobehavioral subsystems with four general categories of affective temperaments, which is divided into twelve global configurations. This complex AFECTS system allows clinicians and researchers to assess underlying emotional and temperamental factors associated with specific disorders in a finer grained fashion. Using this system, Lara and his collaborators are able to identify both the similarities and differences between depression, bipolar disorder, and BPD. All three disorders interface with characteristics of low volition, low coping, and high anxiety. BPD subjects maintain a profile of very high anger and desire as well as low coping and stability. Depressed subjects show lower anger and desire and higher coping and stability than those with BPD, but higher anger and desire and lower coping and stability than controls. These findings suggest that depression involves mild or moderate variations of features related to anger and coping, while BPD involves more severe variations. Similarly, BPD and bipolar subjects shared the same profile, but with higher anger scores distinguishing those with BPD from those with bipolar. In comparison to both mood disorders, BPD involves greater severity of dysfunctional traits.

These simple profiles derived from a complex system analyzing a wide number of temperamental and personality features allow clinicians to focus on key qualities, like high externalizing emotions and low self-regulating traits, as the organizing principles in treatment. However, this approach is limited by its lack of conceptual differentiation of disorders beyond an assessment of superficial description of traits. As noted, the differentiation of bipolar disorder from BPD is only by severity of anger, which may only perpetuate misdiagnosis and confusion between the two diagnoses. Treatment approaches tailored towards dimensional assessments of diagnosis have not been adequately proven, so the effectiveness of this approach in treatment of comorbid disorders is unclear. The clinical utility of dimensional and complex models such as Lara's requires further study.

Yalch, Hopwood, and Zanarini present a model of hyperbolic temperament in BPD, in which the tendency towards intense emotional responses is combined with heightened interpersonal sensitivity. They note that negative affectivity, or a heightened tendency to experience negative emotions, is a heritable, stable trait associated with both depression and BPD and might explain the high level of co-occurrence and familial co-aggregation of these disorders. They also assert that the impulsivity, emotional dysregulation, and interpersonal hypersensitivity characteristics of BPD distinguish it from depression. These three characteristics importantly interact, resulting in what Zanarini and Frankenburg have called "emotional hypochondriasis" defined as "the transformation of unbearable feelings of rage, sorrow, shame, and/or terror into unremitting attempts to get others to pay attention to the enormity of emotional pain that one feels" [22]. Impulsive behaviors function as a way to remedy intense emotional pain as well as communicate interpersonally a bid for help, engaging another person to help regulate emotions. This model, for which Yalch, Hopwood, and Zanarini offer some empirical support, identifies more than a set of characteristics in BPD. It provides a model for interactions and functions between elements of the BPD syndrome as well as a model of transactions between an individual's innate vulnerabilities and environment.

The model of hyperbolic temperament in BPD specifies both the overlaps and distinctions between BPD and depression as well as between acute and chronic symptoms of BPD. As Yalch, Hopwood, and Zanarini explain, the negative affectivity in depression confers a general vulnerability to develop negative emotions in response to stress, while in hyperbolic temperament, the vulnerability to intense negative emotion is developmentally rooted in and activated by interpersonal stress. Acute symptoms of BPD – that is, impulsive, self-destructive, and interpersonally focused behaviors – emerge episodically and remit, while temperamental symptoms persist, leading to chronic dysphoria and psychosocial dysfunction [23]. Negative affectivity, according to Yalch, Hopwood, and Zanarini, is a common factor driving vulnerability for and chronic features of both MDD and BPD, while more specific behavioral and interpersonal factors may differentiate manifestation of acute symptoms in the two disorders.

Both chapters represent different frameworks for understanding the interplay of dimensional temperamental and personality features in the development of the clinical presentations that are classified categorically as disorders. While Lara's model

provides a broadly applicable system of analysis used to understand a range of mood disorders in terms of personality features, it lacks a more theoretical formulation for the coexistence and interplay of these features. His model may help clinicians to identify specific features which can be targeted in diagnostically nonspecific therapeutic interventions (i.e., medications and cognitive behavioral therapy), but is largely empirical and descriptive. In contrast, the model described by Yalch, Hopwood, and Zanarini is more specific to BPD, a single disorder, but provides a formulation for how the symptoms of the disorder interact, thereby allowing clinicians to base their interaction with patients in treatment around not only a description of their problems but a theory about the nature and source of those problems. This transactional formulation of BPD is organized much like that of Linehan's biosocial theory [24] and Bateman and Fonagy's developmental theory of BPD [25], which explain how symptoms and underlying vulnerabilities interact. These theoretical understandings of BPD have been useful in developing organized psychosocial treatments.

Both approaches are necessary and limited. The more descriptive approach used in the mood disorder literature allows researchers and clinicians to identify stable temperamental and personality characteristics influencing vulnerability towards mood states and disorders, but does not provide a clear theory to organize therapeutic interventions. Importantly, these models and assessments appear to be effective in differentiating depression from bipolar disorder but less effective in differentiating bipolar disorder from BPD, leading the proponents of the bipolar spectrum to assume this means BPD represents a form of bipolar disorder. Transactional models, as represented by Yalch, Hopwood, and Zanarini, provide more elaborated theory of the interface between personality or temperamental features and symptomatic clinical features. However, these are far more specific to BPD as a single disorder and therefore limited in their utility for the generalist practitioner. In order to bridge the differences between the frameworks used in both realms of psychiatry, it will be important to standardize instruments and methodologies to relate research findings and test clinical applications. Further research is needed to understand the broad implications of temperament and personality in terms of liability for both mood disorders and BPD with emphasis on identifying systems of assessment which can be reliably and practically implemented in clinical settings. Special attention is needed to ensure that efforts to dimensionalize diagnostic assessments improve rather than undermine established treatment guidelines.

Clinical Evaluation and Staging for Prescribing Interventions: Mitigating Premature Diagnostic Certainty and Therapeutic Overkill

The emergence of identifiable risk factors, precursors, and early symptoms of both mood and borderline personality disorders commonly occurs during the developmental period between adolescence and early adulthood. Chanen and Thompson

highlight the difficulty attaining diagnostic clarity in the face of evolving symptomatology that may be sub-syndromal and nonspecific. In their review of the literature, Chanen and Thompson report that childhood adversity – specifically childhood maltreatment, trauma or stressful life events, and socioeconomic disadvantage – increases risk for various psychiatric diagnoses. These factors in themselves are not differentiating in diagnosis. The early signs and precursors to mood and borderline personality disorders overlap significantly, which is consistent with what has been noted throughout this book about later stage and fully developed variants of these disorders. Bipolar disorder and BPD in younger patients present with risk factors and comorbidity such as childhood disruptive behavioral disorders (e.g., ADHD) and substance abuse as well as personality traits such as impulsivity and emotional dysregulation. Early-onset depression is common in both BPD and bipolar disorder; therefore, depression is not specific to either diagnostic entity. Hypomanic and depressive symptoms are common in this developmental period. Specifically, recurrence or persistence of symptoms, rather than single episodes of mood symptoms, is predictive of the development of psychiatric syndromes at clinically significant levels warranting diagnosis and intervention.

Chanen and Thompson acknowledge the need for early intervention in all diagnostic scenarios as delays in making a diagnosis of bipolar disorder or BPD necessarily delay the access to appropriate treatment. However, in the face of the usual clinical ambiguity commonly encountered in general practice, clinicians may be pressed to err on the side of either premature diagnostic certainty or delay in making proper diagnoses. Chanen and Thompson propose a clinical staging approach to accommodate the possibility of starting with an uncertain stance towards diagnosis which can be carefully refined with longitudinal clinical observation. Furthermore, Chanen and Thompson criticize the tendency in both child and adult clinical psychiatry settings to select the most intensive interventions as first line rather than those scaled towards clinical presentation. Their clinical staging approach provides lower intensity, broad interventions with specific indications for more intensive treatments which may be otherwise unclear in their indications, problematic in terms of side effect burden, or too resource intensive to be widely available to the public.

Chanen and Thompson's model of clinical staging can potentially mitigate premature diagnostic certainty and therapeutic overkill in both child and adult settings. As they note in their chapter, "[t]he reification of each separate syndrome leads to the implication that one clinician or another is missing an 'obvious case' and has foolishly applied the 'wrong' treatment or is denying much needed specific treatment" (166). This tendency leads to defensiveness and mistrust among clinicians as well as among patients and their families and presents added challenges to effective treatment regardless of ultimate diagnosis. Even when a proper diagnosis of BPD is made, the most intensive therapeutic approaches are often prematurely recommended, leading to misallocation of scarce treatment resources to those who can access it, rather than to those for whom intensive treatments are clinically indicated.

Psychopharmacologic and Psychotherapeutic Interventions: Priorities and Compromises

Current psychiatric evidence and practice guidelines suggest the following: (1) bipolar disorder responds primarily to psychopharmacologic treatment, and psychotherapy is adjunctive; (2) BPD responds primarily to psychotherapeutic interventions, and psychopharmacology is adjunctive; and (3) depression responds to both psychopharmacology and psychotherapy. Our discussion in this book has helped us to arrive at some paradoxes in the relationships between these disorders. The first paradox is that while depression and BPD are highly comorbid and overlap in underlying liabilities and biological processes, BPD does not consistently respond to antidepressant medication. The second paradox is that while bipolar disorder and BPD are superficially similar and fundamentally different, many elements of their standard treatments (i.e., mood stabilizers and psychotherapy) overlap. Understanding the complexities of the relationships between these disorders in particular and between mood, personality, and temperament more broadly will enable clinicians to effectively map the shared territories among these clinical concepts and fashion an organized and flexible treatment plan.

Major depression is a heterogeneous disorder with multiple subtypes and responds to a number of interventions comparably, including placebo, St. John's wort, psychotherapy, and antidepressant medication [26, 27]. While depression by itself typically remits with a variety of treatments, it does not remit in cases of comorbid BPD until BPD improves [28]. Comorbidity with BPD may in itself be a marker of more severe and chronic psychopathology which confers increased risk for chronicity and recurrence of mood problems. As noted by Silk in his chapter, antidepressant medications may ameliorate typical symptoms of depressive episodes as a distal outcome of shared vulnerabilities between depression and BPD, but do not target underlying vulnerabilities towards negative affectivity, emotional dysregulation, and interpersonal sensitivity, which are liabilities increasing risk for both disorders. Careful assessment of what is meant by depression, as recommended by Silk in his chapter, must be assessed to guide the decision of whether or not medication is indicated. Psychosocial approaches target these underlying vulnerabilities more specifically, whereas antidepressants appear to relieve more superficial and episodic symptoms. Additionally, some evidence exists suggesting psychotherapy is more effective than antidepressant medication in the treatment of patients with depression and history of early life stress [29]. Underlying vulnerabilities and environmental stressors interact to increase risk for both depression and BPD; therefore, treatment should aim to address these factors, not just acute symptoms of depression or BPD.

A variety of intensive psychotherapeutic approaches designed specifically for BPD have been found effective in decreasing suicidality, self-harm, depressive symptoms, and utilization of acute medical and psychiatric services (see Gunderson et al. [33] for review). The most prominent of these – Dialectical Behavioral Therapy (DBT), Mentalization-Based Treatment (MBT), Transference-Focused

Psychotherapy (TFP), and Schema-Focused Psychotherapy (SFT) – involve at least three to five hours of treatment weekly in the formats they have been found effective. Currently, a number of less intensive psychosocial or clinical management interventions, which include cognitive behavioral therapy (CBT), supportive psychotherapy, structured clinical management (SCM), and General Psychiatric Management (GPM), have been found to be comparable in reducing symptomatology to the more intensive evidence-based modalities described above, but require less specialized training and are more generalizable to nonspecialist settings [30–33]. While some of these treatments may have less robust effects on reducing symptoms of BPD and depression, they are more practical as first-line interventions for patients with BPD and mood disorder comorbidity. There is also limited evidence that a generalist approach (i.e., GPM) may lead to lower rates of drop out in cases of axis I comorbidity compared to a more intensive treatment such as DBT [34]. More intensive treatments might be reserved for patients who fail to respond to these first-line interventions. Efforts to train mental health clinicians broadly in less intensive approaches for BPD are essential so that access to care is broadened. Lastly, research efforts are needed to clarify the effectiveness of step-wise approaches based on clinical staging as proposed by Chanen and Thompson that guide prescription and allocation of these forms of care.

The chapters on psychotherapeutic interventions for BPD and mood disorders included in this book focus on more generalizable flexible frameworks that can be widely disseminated to mental health clinicians of all disciplines and adjusted for a wide range of emotional problems. Jacob and Rodriguez-Villa describe the adaptation of CBT for a wide range of emotional problems. They identify interpersonal vulnerabilities and instabilities in self-awareness as key clinical features in BPD which limit the effectiveness of general CBT interventions aimed at specific anxiety or mood disorders. DBT and SFT provide important adaptations to the specific treatment challenges for clinicians working with patients with BPD. Attention to psychoeducation about the BPD diagnosis, strategies to stabilize and increase self-awareness (e.g., mindfulness and self-assessment), and a focus on interpersonal patterns are common features of evidence-based treatments (EBTs) for BPD which can be easily adapted into a more general CBT framework. More research is needed to test this adapted CBT approach in working with patients with mixed presentations of BPD and mood disorders.

Luyten and Fonagy describe the adaptation of psychodynamic approaches to patients with MDD and BPD, based on assessments of depressive features, mentalizing capacities, stability of attachment functioning, and capacities for epistemic trust. Like Jacob and Rodriguez-Villa, Luyten and Fonagy contend that reflective and relational capacities complicate general psychotherapeutic approaches. Luyten and Fonagy additionally note that treatments which presume a stable capacity for mentalization may be iatrogenic for patients with BPD. In their chapter, they present a spectrum of mentalizing approaches which can be flexibly applied to individuals with depression without BPD and those with both BPD and depression. For both categories of patients, mentalizing approaches ultimately focus on affective experiences in interpersonal contexts. However, intensive full-scale MBT is needed for

patients with BPD as special attention is needed for assessment and stabilization of mentalizing capacities and attachment activation. The MBT approach provides a generalizable treatment framework which can be adjusted for severity of reflective and interpersonal dysfunction; therefore, MBT may be an approach that can be adapted, like CBT, to a wider range of disorders.

The overlap between treatments for bipolar and borderline personality disorders is more superficial. Both disorders respond to mood stabilizers and atypical antipsychotics, but even in bipolar disorder where medications are primary interventions, a minority of patients achieve remission with these agents. While evidence exists for the efficacy of mood stabilizers in reducing a variety of symptoms relevant to BPD, the literature is both limited and inconclusive, lacking rationale to designate any indication for any specific medication. The underlying processes for these disorders are mostly divergent, although cyclothymic temperament may increase liabilities for both diagnoses, as noted by Choi-Kain and Rodriguez-Villa in their chapter. In general, the basic mechanism in bipolar disorder related to the development of manic states is most reliably responsive to mood stabilizers and not likely to respond to psychotherapy alone. Conversely, the core vulnerabilities to emotional dysregulation in the face of interpersonal hypersensitivity are more responsive to appropriate psychosocial intervention and unlikely to respond to medication alone. In both diagnoses, the standards for treatment of depressive states remain unclear. However, as several authors have noted throughout this book, depressive symptoms improve when BPD improves in comorbid states.

Psychosocial approaches are clearly indicated for BPD, but are adjunctive for bipolar disorder. Studies of psychotherapeutic approaches to bipolar disorder are limited but demonstrate a role for reducing relapse (particularly to depression) and improving functionality [35]. Jacob and Rodriguez-Villa identify psychoeducation, problem-solving, support, coping, and self-care skills as common features of validated psychotherapies for bipolar disorder and BPD. These features focus on enhancing self-awareness and interpersonal stability [35]. The techniques inherent in different psychosocial treatments for these various diagnoses appear to differ not in content but in organization around core vulnerabilities and symptomatic problems. This suggests that what may make treatments work is an integration of therapeutic technique with a clear theory of the essential nature of the patient's problems.

While psychopharmacologic interventions are necessary and critical to the management of mood disorders, their use is often accompanied by unrealistic expectations, regardless of the diagnosis. Studies on trends in management of psychiatric disorders demonstrate an increase in long-term use of antidepressant medications without adequate knowledge of the risks associated with more prolonged use [36, 37]. There is also evidence that antidepressant use without psychiatric diagnosis is also on the rise, despite controversy about their superiority over placebo for depression [38–42]. With more complex clinical presentations involving comorbidity, there is a tendency for polypharmacy, which is largely unguided by treatment algorithms or evidence. This pattern of increased polypharmacy without the constraints of clinical guidelines or evidence poses undue risk for side effects and drug

interactions in the face of unclear benefits [43]. Clinicians and patients alike would benefit from more tempered and realistic understanding of what pharmacologic treatments can offer, regardless of diagnosis.

Concomitantly, there has been a significant decline in the practice of psychotherapy by psychiatrists, likely due to changes in insurance reimbursement and the predominance of psychopharmacologic intervention in the field [44]. Problematically, studies suggest that psychiatrists specializing in psychotherapy primarily see patients who can self-pay, while those who primarily prescribe medications "shun delivery of psychotherapy altogether" [44]. Evidence suggests that patients prefer psychological treatments over pharmacologic treatments for a variety of diagnoses, including depression, bipolar disorder, and BPD [45]. Depression, bipolar disorder, and BPD all respond to psychotherapeutic interventions though access to specialized intensive treatment is limited. In this era of declining practice of psychotherapy by psychiatrists, structured clinical or general management approaches are needed to broaden access to care for patients with complex comorbidities, particularly those with BPD. More training is necessary to provide generalists with strategies to manage the complexities and comorbidities of patients with BPD.

Current Status and Future Directions

In the last two decades, the scientific progress in understanding the boundaries and overlaps between mood and borderline personality disorders has been significant. This book represents an attempt to review that progress. What is clear is that the older strain of dialogue between the voices of the mood disorder and personality disorder camps has segued from a contentious debate to a parallel but marginally interactive inquiry about the relationship between personality, temperament, biological processes, diagnostic entities, and treatment. On both sides, the interaction between personality factors and depression is widely recognized. Significant investigations on how to model these relationship both empirically and theoretically have been pursued, but more effort for cross-pollination of these investigations is necessary, using more streamlined methodologies to link the findings in both arenas. In contrast, the efforts to incorporate BPD into the bipolar spectrum have been slowed by increasing evidence that these disorders are only superficially similar while they are etiologically and fundamentally distinct. While the overlap between bipolar type II and BPD needs to be clarified, the consensus in this book is that the current state of knowledge allows clinicians clear indices of differentiating these disorders.

However, despite the increasing clarity on the distinction between these disorders, clinicians routinely encounter evolving, atypical, subthreshold, comorbid cases which are inherently difficult to diagnose. Chanen's clinical staging approach provides a framework for guiding clinicians to scale their interventions for clinical severity, so that clinicians are not pressured into false diagnostic certainty for early stage or ambiguous cases. While the advance of research has established effective treatments for both mood and borderline personality disorders, many of these

treatments are heavy handed. Psychopharmacologic treatments are replete with side effects, risk teratogenicity, and can be lethal in overdose. Psychosocial treatments that are held to be the gold standard for BPD are both too intensive and specialized for most generalist mental health practitioners to administer, so clinicians and patients face a serious dearth of accessible treatment for this disorder. More effort is needed to develop and proliferate more flexible and less intensive treatments for BPD. Research on and training for more generalizable psychosocial approaches that clinicians can adapt to a variety of common and comorbid mood and personality problem, such as CBT and mentalizing treatments, is needed. These more generalizable approaches might focus on shared personality features such as emotional dysregulation and interpersonal sensitivity as broadly relevant factors that contribute to risk for developing psychiatric illness more generally and in its most severe form, BPD.

The controversy about the distinctions and overlaps between mood and borderline personality disorders has unfolded in the context of a greater landscape in psychiatry, where the limitations of descriptive approaches to diagnosis have been highlighted by the reality of pervasive comorbidity, atypical variants, and misdiagnosis. The DSM-V revision was organized initially with an ambitious move towards efforts to refine diagnostic systems based on etiological rather than descriptive factors; however, adequate scientific clarity could not be achieved to make that needed shift. The current status of this dilemma relevant to the subject of this book suggests that the effort to bridge and integrate the fields of scientific inquiry and treatment strategies between the mood and personality sectors of the field is a more immediate and practical possibility. This integration enables a synthesis rather than division of efforts to more properly and comprehensively understand and treat these disorders and the patients who have them.

References

1. Stone MH. Assessing vulnerability to schizophrenia or manic-depression in borderline states. Schizophr Bull. 1979;5(1):105–10.
2. Akiskal H, Chen SE, Davis GC, Puzantian VR, Kashgarian MM, Bolinger JM. Borderline: an adjective in search of a noun. J Clin Psychiatry. 1985;46(2):41–8.
3. Gunderson JG, Elliott GR. The interface between borderline personality disorder and affective disorder. Am J Psychiatry. 1985;142(3):277–88.
4. Zanarini MC, Frankenburg FR, Dubo ED, Sickel AE, Trikha A, Levin A, et al. Axis I comorbidity of borderline personality disorder. Am J Psychiatry. 1998;155:1733–9.
5. McGlashan TH, Grilo CM, Skodol AE, Gunderson JG, Shea MT, Morey LC, et al. The Collaborative Longitudinal Personality Disorders Study: baseline Axis I/II and II/II diagnostic co-occurence. Acta Psychiatr Scand. 2000;102(4):256–64.
6. Sass H, Junemann K. Affective disorders, personality and personality disorders. Acta Psychiatr Scand Suppl. 2013;108(S418):34–40.
7. Links PS, Steiner M, Huxley G. The occurrence of borderline personality disorder in the families of borderline patients. J Pers Disord. 1988;2:14–20.
8. Zanarini MC, Gunderson JG, Marino MF, Schwartz EO, Frankenburg FR. DSM-III disorders in the families of borderline outpatients. J Pers Disord. 1988;2:292–302.

9. Silverman JM, Pinkham L, Horvath TB, Coccaro EF, Klar H, Schear S, et al. Affective and impulsive personality disorder traits in the relatives of patients with borderline personality disorder. Am J Psychiatry. 1991;148:1378–85.
10. Krueger RF, Caspi A, Moffitt TE, Silva PA. The structure and stability of common mental disorders (DSM-II-R): a longitudinal-epidemiological study. J Abnorm Psychol. 1988;107:216–27.
11. Kessler RC, Ormel J, Petukhova M, McLaughlin KA, Green JG, Russo LJ, et al. Development of lifetime comorbidity in the World Health Organization world mental health surveys. Arch Gen Psychiatry. 2011;68(1):90–100.
12. Kotov R, Ruggero CJ, Krueger RF, Watson D, Yuan Q, Zimmerman M. New dimensions in the quantitative classification of mental illness. Arch Gen Psychiatry. 2011;68(10):1003–11.
13. Roysamb E, Kendler KS, Tambs K, Orstavik RE, Neale MC, Aggen SH, et al. The joint structure of DSM-IV Axis I and Axis II disorders. J Abnorm Psychol. 2011;120(1):198–209.
14. Hudson JI, Javaras KN, Laird NM, VanderWeele TJ, Pope HG, Hernan MA. A structural approach to the familial coaggregation of disorders. Epidemiology. 2008;19(3):431–9.
15. Gunderson JG, Phillips KA. A current view of the interface between borderline personality disorder and depression. Am J Psychiatry. 1991;148:967–75.
16. Koenigsberg HW, Anwunah I, New AS, Mitropoulou V, Schopick F, Siever LJ. Relationship between depression and borderline personality disorder. Depress Anxiety. 1999;10(4):158–67.
17. Akiskal HS, McKinney Jr WT. Depressive disorders: toward a unified hypothesis. Science. 1973;182(4107):20–9.
18. Blatt SJ, Zuroff DC. Interpersonal relatedness and self-definition: two prototypes for depression. Clin Psychol Rev. 1992;12(5):527–62.
19. Gunderson JG, Lyons-Ruth K. BPD's interpersonal hypersensitivity phenotype: a gene-environment-developmental model. J Pers Disord. 2008;22.
20. Choi-Kain LW, Fitzmaurice GM, Zanarini MC, Laverdiere O, Gunderson JG. The relationships between self-reported attachment styles, interpersonal dysfunction, and borderline personality disorder. J Nerv Ment Dis. 2009;197(11):816–21.
21. Staebler K, Helbing E, Rosenbach C, Renneberg B. Rejection sensitivity and borderline personality disorder. Clin Psychol Psychother. 2011;18(4):275–83.
22. Zanarini MC, Frankenburg FR. Emotional hypochondriasis, hyperbole, and the borderline patient. J Psychother Pract Res. 1994;3:25–36.
23. Zanarini MC, Frankenburg FR, Reich DB, Silk KR, Hudson JI, McSweeney LB. The subsyndromal phenomenology of borderline personality disorder a 10-year follow-up study. Am J Psychiatry. 2007;164(6):929–35.
24. Linehan MM. Cognitive behavioral treatment of borderline personality disorder. New York: Guilford Press; 1993.
25. Bateman A, Fonagy P. Psychotherapy for borderline personality disorder: mentalization based treatment. Oxford: Oxford University Press; 2004.
26. Parker G, Manicavasgar V. Modelling and managing the depressive disorders: a clinical guide. New York: Cambridge University Press; 2005.
27. Gaynes BN, Warden D, Trivedi MH, Wisniewski SR, Fava M, Rush AJ. What Did STAR*D Teach Us? Results from a large-scale, practical, clinical trial for patients with depression. Psychiatr Serv. 2009;60(11):1439–45.
28. Gunderson JG, Morey LC, Stout RL, Skodol AE, Shea MT, McGlashan TH, et al. Major depressive disorder and borderline personality disorder revisited: longitudinal interactions. J Clin Psychiatry. 2004;65:1049–56.
29. Nemeroff CB, Heim CM, Thase ME, Klein DN, Rush AJ, Schatzberg AF, et al. Differential responses to psychotherapy versus pharmacotherapy in patients with chronis forms of major depression and childhood trauma. Proc Natl Acad Sci U S A. 2003;100(24):14293–6.
30. Davidson K, Norrie J, Tyrer P, Gumley A, Tata P, Murray H, et al. The effectiveness of cognitive behavior therapy for borderline personality disorder: results from the borderline personality disorder study of cognitive therapy (BOSCOT) trial. J Pers Disord. 2006;20(5):450–65.
31. McMain SF, Links PS, Gnam WH, Guimond T, Cardish RJ, Korman L, et al. A randomized trial of dialectical behavior therapy versus general psychiatric management for borderline personality disorder. Am J Psychiatry. 2009;166(12):1365–74.

32. Clarkin JF, Levy KN, Lenzenweger MF, Kernberg OF. Evaluating three treatments for borderline personality disorder: a multiwave study. Am J Psychiatry. 2007;164(6):922–8.
33. Gunderson JG, Weinberg I, Choi-Kain L. Borderline personality disorder. Focus. 2013;11: 129–45.
34. Wnuk S, McMain S, Links PS, Habinski L, Murray J, Guimond T. Factors related to dropout from treatment in two outpatient treatments for borderline personality disorder. J Pers Disord. 2013;27(6):716–26.
35. Lauder SD, Berk M, Castle DJ, Dodd S, Berk L. The role of psychotherapy in bipolar disorder. Med J Aust. 2010;193(4 Suppl):S31–5.
36. Mojtabai R, Olfson M. National trends in long-term use of antidepressant medications: results from the US National Health and Nutrition Examination Survey. J Clin Psychiatry. 2014;75: 169–77.
37. Fava GA, Offidani E. The mechanisms in antidepressant action. Prog Neuropsychopharmacol Biol Psychiatry. 2011;35(7):1593–602.
38. Mathew SJ, Charney DS. Publication bias and the efficacy of antidepressants. Am J Psychiatry. 2009;166(2):140–5.
39. Khan A, Bhat A, Kolts R, Thase ME, Brown W. Why has the antidepressant-placebo difference in antidepressant clinical trials diminished over the past three decades? CNS Neurosci Ther. 2010;16(4):217–26.
40. Kirsch I, Deacon BJ, Huedo-Medina TB, Scoboria A, Moore TJ, Johnson BT. Initial Severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. PLoS Med. 2008;5(2):e45.
41. Fournier JC, DeRubeis RJ, Hollon SD, Dimidjian S, Amsterdam JD, Shelton RC, et al. Antidepressant drug effects and depression severity: a patient-level meta-analysis. JAMA. 2010;303:47–53.
42. Pagura J, Katz LY, Mojtabai R, Druss BG, Cox B, Sareen J. Antidepressant use in the absence of common mental disorders in the general population. J Clin Psychiatry. 2011;72(4): 494–501.
43. Mojtabai R, Olfson M. National trends in psychotropic medication polypharmacy in office-based psychiatry. Arch Gen Psychiatry. 2010;67(1):26–36.
44. Mojtabai R, Olfson M. National trends in psychotherapy by office-based psychiatrists. Arch Gen Psychiatry. 2008;65(8):962–70.
45. McHugh RK, Whitton SW, Peckham AD, Welge JA, Otto MW. Patient preference for psychological vs pharmacologic treatment of psychiatric disorders: a meta-analytic review. J Clin Psychiatry. 2013;74(6):595–602.

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