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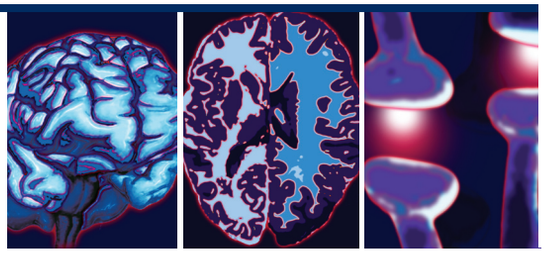

Differential diagnosis of bipolar and borderline personality disorders

Joel Paris[†]

Practice points

- Differential diagnosis in psychiatry is problematic because it depends on observable signs and symptoms rather than on biological markers.
- The bipolar spectrum
  – Proposals to expand the bipolar spectrum are based almost entirely on phenomenological resemblances; evidence for common family history, outcome and treatment response is very weak.
  – Mood swings need not necessarily reflect bipolarity.
  – Hypomania needs to be carefully assessed for time scale and persistence.
- Affective instability
  – Affective instability is a separate construct from bipolarity and has developed its own emerging research literature.
- Borderline personality disorder
  – Borderline personality disorder is a complex diagnosis characterized by mood instability, impulsivity and disturbed relationships.
  – The affective instability in borderline personality disorder does not resemble classical bipolar disorders, and can be distinguished from hypomania.
- Treatment implications
  – Treatment of bipolar II disorder requires mood stabilizers, while clinical trials show that borderline personality disorder is most effectively managed with specialized psychotherapy.
- Conclusion
  – Differences in treatment options make differential diagnosis of these disorders clinically important.

SUMMARY The hypothesis that many mental disorders fall within a bipolar spectrum, and that the mood instability that characterizes borderline personality disorder puts it into this spectrum is critically reviewed. This conclusion is based on phenomenological resemblances, and does not consider differences in course, outcome and treatment. Careful evaluation of hypomania is required to diagnose bipolar II disorder. Affective instability is

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a different phenomenon that characterizes borderline personality disorder. Differential diagnosis is important because bipolar disorders require medication, while borderline personality disorder is most effectively managed with specialized forms of psychotherapy.

Differential diagnosis in psychiatry

Classification in psychiatry is problematic because diagnosis is not based on an understanding of etiological and pathogenetic mechanisms, but on observable signs and symptoms. Hardly any of the disorders diagnosed by psychiatrists are consistently correlated with biological markers [1,2].

In medicine, similar symptoms can derive from entirely different causes. Clustering of symptoms describes a syndrome, not a disease process. In the absence of precise and specific laboratory tests, all categories in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) system, including bipolar disorder, can only be regarded as provisional.

Yet diagnostic categories can become popular for reasons other than validity. In the history of medicine, diagnoses may be preferred when new methods of treatment become available [3]. The usefulness of lithium and other mood stabilizers for the acute treatment of mania and for prevention of relapse led psychiatrists to reconsider whether patients in other categories might suffer from a form of bipolar disorder [4].

This article will examine whether the evidence supports the spectrum concept, and whether the spectrum includes borderline personality disorder.

The bipolar spectrum

Recent suggestions to extend the boundaries of bipolar disorder to a broad spectrum [5,6] led to a radically different concept of bipolarity. The assumption that mood swings, including cases marked more by irritability than by euphoria, justify a bipolar diagnosis requires the invocation of a construct of 'soft bipolarity' (i.e., a variant or subclinical form of classical bipolar disorder) [7]. However, the expanded spectrum is defined entirely on the basis of phenomenological resemblances, and not on etiology or pathogenesis.

Emil Kraepelin defined manic-depressive illness, later renamed bipolar disorder [8]. Since then, manic episodes have always required a classical triad of symptoms: elevated affect, psychomotor excitement and racing thoughts. Classically, psychiatrists would not diagnose mania or hypomania in the absence of euphoria. However, after the introduction of lithium, it was observed that some patients who respond to that drug had atypical features such as irritability. That observation led to questions as to whether states of excitement, irritability and aggression, seen in other categories of disorder, are symptoms of mania, and whether the classical triad is a necessary condition for diagnosis [5,6].

The concept of a bipolar spectrum is similar to that of a schizophrenic spectrum [9], in which psychopathology can range from severe disabling illness to problems that appear to be 'characterological'. The first person to suggest that a bipolar spectrum exists was Kraepelin [8], who described subclinical cases in first-degree relatives of affected patients. But Kraepelin's concept has been greatly broadened, with some surveys claiming that up to 30% of all psychiatric patients have a form of soft bipolarity [10].

The most generally accepted variant of the classical picture is bipolar II disorder [11]. This diagnosis describes mood swings from depression to hypomania rather than to full mania. This patient population is heterogeneous, in that only a few have a family history of bipolar disorder, and not all cases respond to mood stabilizers [12].

Some cases of bipolar II also meet criteria for personality disorders [13]. However, this overlap may not reflect true comorbidity, but diagnostic biases. Criteria for bipolarity can be quite broad, and epidemiological studies have sometimes considered all cases in which mood swings are observed as either bipolar II or bipolar spectrum disorders [14].

The key issue lies in the assessment of hypomania. In the DSM-IV-TR [15], this syndrome is defined as "a distinct period of persistently elevated, expansive, or irritable mood, lasting throughout at least 4 days, that is clearly different from the usual nondepressed mood". Patients must then have at least three of the following (four if the mood is irritable and not euphoric): inflated self-esteem or grandiosity, decreased need for sleep, more talkative than usual or pressure to keep talking, flight of ideas or subjective experience that thoughts are racing, distractibility, increase in goal-directed activity (either socially, at work or school, or

sexually) or psychomotor agitation, and excessive involvement in pleasurable activities that have a potential for painful consequences. Finally, and crucially, a hypomanic episode must be associated with an unequivocal change in functioning that is uncharacteristic of the person when not symptomatic, and should be observable by other people. In contrast to full mania, hypomania need not be severe enough to cause marked impairment in social or occupational functioning, rarely necessitates hospitalization and is not associated with psychotic symptoms.

In short, hypomanic episodes have requirements defined by severity, time scale, and persistence. If one follows DSM criteria strictly, one could not make a bipolar II diagnosis in patients whose mood swings last less than 4 days, or in whom mood does not remain abnormal over the entire period. It has been suggested that the 4-day rule is arbitrary [16]. This is true, but any other rule would be equally arbitrary. DSM-5 will appear in 2013 [17], and a 2-day rule may be accepted, but that change would not affect the diagnosis of patients who experience mood swings on a daily or an hourly basis.

Another variant of bipolar disorder in DSM-IV-TR is a 'mixed state', defined as at least a week in which a patient meets criteria for both major depression and mania. The research on this category is rather thin, and although some cases may be bipolar [18], the category can be used to describe a heterogeneous group of angry and/or agitated patients.

The DSM-IV-TR also allows for a diagnosis of bipolar disorder, not otherwise specified. Like other groupings in the manual, the not otherwise specified category describes patients with some but not all features of the disorder. In practice, it could be used to diagnose almost any patient with mood swings.

In a formal proposal to describe the spectrum [19], it has been suggested that bipolarity can take four basic forms: bipolar I, the classical manic-depressive category described by Kraepelin; bipolar II, depression with spontaneous hypomanic episodes; bipolar III, in which hypomanic episodes occur only after taking antidepressants; and bipolar IV, an ultra-rapid-cycling disorder. The last category would include many personality disorders, as well as children with mood instability.

Another suggestion describes even more forms of bipolar disorder [20]: bipolar I, full-blown mania; bipolar I½, depression with protracted hypomania; bipolar II, depression with hypomanic episodes; bipolar II½, cyclothymic disorder; bipolar III, hypomania due to antidepressant drugs; bipolar III½, hypomania and/or depression associated with substance use; bipolar IV, depression associated with hyperthymic (i.e., mood) temperament; bipolar V,: recurrent depressions mixed with dysphoric hypomania; and bipolar VI, late-onset depression with mixed mood features, progressing to a dementia-like syndrome. These expanded definitions inevitably lead to high estimates of prevalence.

None of these proposals are based on a gold standard for bipolarity or on consistent biological markers derived from genetics or neurobiology (which, in any case, do not exist). Instead, epidemiological and clinical studies have examined the prevalence of spectrum disorders using scales designed to assess symptoms of soft bipolarity, identifying cases through the presence of subthreshold symptoms [14]. But it is equally possible that moodiness reflects a different phenomenon, not related to classical mood disorders.

How can one validate the bipolar spectrum, if no specific biological markers are known? Kraepelin's original definition of manic-depression was based on long-term outcome, yet more research would be needed to show that the course of putative spectrum conditions is similar to what Kraepelin described for mood episodes. Another possibility is to carry out 'pharmacological dissection' [21], in which similar responses to treatment suggest common endophenotypes. Yet clinical trials are needed to show that the drugs used to treat bipolar disorder are effective in putative spectrum disorders [22]. It is equally possible that the affective symptoms in spectrum conditions may be a different phenomenon based on a different mechanism.

Affective instability

When mood swings are associated with consistent changes in grandiosity energy, psychomotor activity, and sleep, then it may be reasonable to see them as lying in the bipolar spectrum. But in the absence of these features, the main alternative is the construct of affective instability (AI) [23], also called emotion dysregulation [24]. AI describes brief mood changes characterized by temporal instability, high intensity and delayed recovery from dysphoric states. The construct emphasizes a distinction between environmentally driven, short-duration mood swings (AI) versus spontaneous, long-duration

mood swings (bipolar and unipolar mood disorders). Although research on AI is still in its early stages, it can be reliably measured and separated from mood intensity [25], has been shown to be distinct from neuroticism [26] and is a heritable trait [27].

Affective instability is a common feature of personality disorders, particularly the borderline category [28,29]. Studies of patients diagnosed with borderline personality disorder (BPD) document rapid shifts in mood, qualitatively different from those seen in bipolar II disorder [30,31]. Thus, mood swings from depression to anger are seen, while euphoria is rare. Crucially, AI is highly sensitive to environmental cues and interpersonal stressors [26]. Finally, family studies of patients with BPD (with severe AI) find that diagnoses reflecting impulsivity, such as substance abuse and antisocial personality, are common in first-degree relatives, with unipolar depression being somewhat less common, and bipolar disorders rare [32]. Some research suggests that AI can be associated with a unique pattern of activity in functional imaging, and with unique changes in neurotransmitter activity [23].

All this research suggests that affective instability reflects a unique endophenotype. While it is possible that some patients with personality disorders share neurobiological predispositions with bipolar patients, one cannot assume that all (or most) do.

Borderline personality disorder

Borderline personality disorder is a complex multidimensional disorder characterized by emotion dysregulation, impulsivity and unstable relationships [33]. The label 'borderline' is outdated (derived from a theory that psychopathology can fall on a border between psychosis and neurosis). However, BPD is a clinically important disorder. It affects nearly 1% of the community population [34,35], and is common in emergency rooms and out-patient clinics [33].

While BPD shows extensive comorbidity, its wide range of symptoms reflects severe personality pathology. Major depression is particularly common, and these symptoms are usually what bring patients to clinical attention [36]. In the past, mood disorder researchers [37] saw BPD as an atypical form of unipolar depression. But depressive symptoms do not show the same pattern in BPD: they are chronic rather than episodic, associated with a mercurial and fluctuating mood that is highly responsive to interpersonal life events [13]. Moreover, BPD patients show higher levels of impulsivity than patients with depression alone [31], and have characteristic symptoms such as self-harm and recurrent overdoses that are uncommon in major depression. Finally, depressive symptoms show only marginal improvement with antidepressants, and these agents never lead to remission of the disorder [33].

Akiskal has now proposed that BPD falls within the bipolar spectrum, largely owing to its prominent affective instability [38]. All other symptoms would be secondary to abnormal mood. There are a number of problems with this hypothesis. First, one sees important differences in time scale and persistence of mood, which can change by the hour, and that respond to vicissitudes in relationships. While it is possible that these reactions are an effect rather than a cause of unstable mood, research using ecological momentary assessment strongly suggests that these patients respond in abnormal ways to interpersonal conflict [26]. By contrast, the idea that AI in BPD reflects spontaneous 'ultra-rapid mood swings' [39] assumes, without sufficient evidence, that all such shifts (or at least a fair percentage) are variants of hypomania or soft bipolarity.

Moreover, the outcome of BPD is very different from (and much more favorable than) bipolar disorder. Whereas classical bipolarity does not remit with age (and often gets worse), the vast majority of BPD patients recover with time, and no longer meet criteria for the disorder by middle age [40]. Therefore, BPD has a relatively good prognosis, and its long-term outcome does not resemble bipolar II disorder.

Another test would be to determine whether BPD responds to the same drugs as bipolar disorder (i.e., mood stabilizers). Only a few clinical trials have examined this question, but by and large, results suggest that the main impact of mood stabilizers in BPD patients is on impulsivity, not on mood. Lithium produces only a mild benefit, mainly in reduction of impulsive symptoms [41], and the findings of clinical trials on carbamazepine [42], divalproex [43], topiramate [44] and lamotrigine [45] are similar. The tendency of drugs to control impulsivity rather than mood is not limited to lithium or anticonvulsant mood stabilizers. Controlled trials of neuroleptics, as well as of selective serotonin reuptake inhibitors in BPD patients, also find more effect on impulsivity than on mood [33].

While these findings do not prove that disorders are separate, they also do not support putting them in the same spectrum.

Differentiating the disorders

In the absence of biological markers, distinguishing disorders that have similar or overlapping symptoms can only be an educated guess. Even so, differences in treatment response make differential diagnosis clinically important.

The key lies in establishing whether a patient has or has not had hypomanic episodes. Patient reports may not be sufficient to answer this question [46]. Furthermore, it is not sufficient to take a brief history from patients who can often be vague about intensity and time scale. Since both false negatives and false positives are possible, it can be helpful to interview family members to determine consistency of symptoms, time scale, whether mood changes lead to behavioral consequences, and whether they are noticeable to others. Shortening the length of time for hypomania, as may occur in DSM-5, would lead to increased diagnoses of bipolar II. However, careful evaluation, supported by the empirical literature [26], shows that BPD patients rarely have consistently elevated (or irritable) mood for as long as 48 h.

The obstacles to accurate differential diagnosis reflect the popularity of the bipolar diagnosis. This is not to say that true bipolar disorders are never misdiagnosed as BPD – they can be. But most cases of BPD are not recognized in practice, and many patients will be called bipolar, even when they do not meet DSM criteria [47]. Clinicians can sometimes have a 'knee-jerk' diagnostic response to mood swings. Many are unfamiliar with the concept of a personality disorder, but receive a continuous stream of claims for bipolar spectrum diagnoses, both from experts who believe in this idea, and from pharmaceutical companies who want to increase sales.

Implications for treatment

Differential diagnosis is important when it leads to different treatment choices. Bipolar I and bipolar II disorder always require medical management. Lithium is still the drug with the strongest support for both types in clinical trials. More research is needed on anticonvulsant mood stabilizers, and some evidence supports atypical neuroleptics as useful adjunctive agents. By contrast, if the diagnosis is BPD, drugs will have only marginal benefits.

While many BPD patients are on polypharmacy regimes, with 4–5 drugs drawn from each major class [48], there is little evidence that this kind of treatment is helpful (not to speak of their long-term side effects). The problem is that a diagnosis of bipolar disorder is likely to lead to the use of multiple pharmacological agents.

Instead, there is good evidence that patients with BPD benefit most from psychotherapies specifically tailored for their symptoms [49]. There is strong evidence for the effectiveness of dialectical behavior therapy [50], and for a similar method, mentalization-based therapy [51]. Research also shows that while unstructured and generic psychotherapies often fail in BPD patients, any method that offers a systematic and well-planned approach can yield favorable results [52].

The main obstacle to effective treatment of BPD lies in a lack of access to psychological services that are expensive and require trained therapists. It is much easier to make a bipolar diagnosis and to write a prescription.

Conclusion & future perspective

While there are insufficient data to reach a final conclusion, researchers advocating an expansion of the bipolar spectrum to include BPD have not proven their case. Recognition of BPD in clinical practice, and differentiation from bipolar II, is of practical importance for effective treatment.

We still have few data on the etiology, pathogenesis, outcome and treatment of bipolar spectrum disorders. Since researchers committed to the validity of the spectrum have conducted many published studies, some of the results could reflect their enthusiasm. Also, research has not taken into account the limitations of phenomenological diagnosis. There is also a need for study of the nature of AI, to establish a clearer boundary between hypomania and emotion dysregulation. Both bipolar II disorder and BPD are heterogeneous disorders: more evidence-based definitions could help to reduce their overlap.

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