

Review Article

Affective instability as rapid cycling: theoretical and clinical implications for borderline personality and bipolar spectrum disorders

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Objectives: The *Diagnostic and Statistical Manual of Mental Disorders* guidelines provide only a partial solution to the nosology and treatment of bipolar disorder in that disorders with common symptoms and biological correlates may be categorized separately because of superficial differences related to behavior, life history, and temperament. The relationship is explored between extremely rapid switching forms of bipolar disorder, in which manic and depressive symptoms are either mixed or switch rapidly, and forms of borderline personality disorder in which affective lability is a prominent symptom.

Methods: A MedLine search was conducted of articles that focused on rapid cycling in bipolar disorder, emphasizing recent publications (2001–2004).

Results: Studies examined here suggest a number of points of phenomenological and biological overlap between the affective lability criterion of borderline personality disorder and the extremely rapid cycling bipolar disorders. We propose a model for the development of ‘borderline’ behaviors on the basis of unstable mood states that sheds light on how the psychological and somatic interventions may be aimed at ‘breaking the cycle’ of borderline personality disorder development. A review of pharmacologic studies suggests that anticonvulsants may have similar stabilizing effects in both borderline personality disorder and rapid cycling bipolar disorder.

Conclusions: The same mechanism may drive both the rapid mood switching in some forms of bipolar disorder and the affective instability of borderline personality disorder and may even be rooted in the same genetic etiology. While continued clinical investigation of the use of anticonvulsants in borderline personality disorder is needed, anticonvulsants may be useful in the treatment of this condition, combined with appropriate psychotherapy.

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In *Manic Depressive Insanity and Paranoia* (1, p. 1), Emil Krapelin writes:

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We include here [in manic-depressive insanity] certain slight and slightest colorings of mood, some of them periodic, some of them continuously morbid, which on the one hand are to be regarded as the rudiment of more severe disorders; on the other hand, pass without sharp

*boundary into the domain of **personal predisposition**. In the course of the years I have become more and more convinced that all the above mentioned states only represent manifestations of a **single morbid process**.*

The adoption of a categorical system for classifying mental disorders – the basis of the current *Diagnostic and Statistical Manual of Mental Disorders* – brought reliability to the clinical diagnosis and study of mental disorder, but at a cost. As with any set of artificially drawn boundaries, some error is bound to occur in the inclusion or exclusion of cases (2). Many patients have symptoms and problems that are typical for a disorder, but do not fall cleanly within the boundaries. The DSM offers a ‘Not Otherwise Specified’ category for such patients, but this designation offers no help to a physician in need of a prognosis for a patient, or to a researcher interested in exploring the causes of the disorder. At the margins, some diagnoses depend on the judgment of the diagnostician, for example, whether a patient is sufficiently impaired by the illness to warrant a diagnosis. On the other hand, some specific diagnostic criteria – those involving duration at the foremost – appear simply arbitrary.

Bipolar disorder is one example of this problem. A 6-day episode of manic symptoms or 13-day episode of depressive symptoms would be of insufficient duration to warrant DSM diagnoses of mania or depression. Does it follow that these too-brief episodes have a different etiology, or require a different form of preventive treatment? What of patients who manifest a mixture of manic and depressive symptoms at the same time, but with insufficient quantities of symptoms of either to meet diagnostic criteria? It seems more parsimonious to assume that such episodes are properly counted as a form of bipolar disorder as well; however, it also seems the more allowances one makes on the diagnostic boundaries, the more likely that disorders with only a superficial resemblance to bipolar disorder will be misdiagnosed as bipolar disorder.

To address bipolar cases with an atypical course, the current diagnostic system provides partial solutions, such as the concept of ‘rapid cycling,’ which serves as a ‘specifier’ in DSM-IV, rather than a discrete type of mood disorder. The DSM-IV defines rapid cycling as the occurrence within 1 year of four or more episodes that meet all criteria for mania, depression, or mixed state. Transitions between episodes must be demarcated either by a 2-month period of full remission or by a switch to an episode of opposite polarity.

Under this or very similar definitions, rapid cycling bipolar disorder has long been studied,

without widespread agreement about its clinical significance (3, 4). While Dunner first identified rapid cycling cases as characteristic of lithium-unresponsive patients (5), later studies have not consistently supported this (6). One study comparing definitions of rapid cycling found poorer prophylactic response to lithium in rapid cycling patients versus non-rapid cycling patients, with the poorest response among the group in which episode duration was waived and all subjects experienced at least one direct polarity switch (7). Similarly, there have been disparate findings as to the association of rapid cycling with illness severity (8–10) and the relationship of rapid cycling to the use of antidepressants (10, 11). One explanation for these discrepancies might be heterogeneity *within* the criteria for ‘rapid cycling.’ Episodes demarcated by full remission may differ in etiologic factors, epidemiologic implications, and therapeutic responsiveness from episodes demarcated by a polarity switch.

In this paper, we critically examine the concept of rapid cycling bipolar disorder, with particular focus on rapidly switching forms of the illness. As such episodes often fail to meet full DSM criteria for rapid cycling bipolar disorder, we place them in the context of the emerging dialogue about bipolar spectrum disorders. We review clinical, neurobiological, demographic, and other features linking bipolar spectrum disorders to other disorders characterized by frequent mood shifts, including borderline personality disorder. We then propose a model for the development of ‘borderline’ behaviors on the basis of unstable mood states and review recent pharmacologic studies suggesting that anticonvulsants may have stabilizing effects in both borderline personality disorder and rapid cycling bipolar disorder. Although cyclothymia is an important part of the bipolar spectrum, the paucity of clinical studies precludes detailed consideration of cyclothymia in this paper.

Limits of the rapid cycling concept

There've been times where I've been cycling so rapidly I was laughing and crying at the same time...one minute way up, the next minute in the total pit of despair, literally mere seconds between the two extremes....soc.support.depression.manic 3/27/01

The diagnosis of rapid cycling hinges on identifying shifts from one mood state to another. In the ideal case, a person with rapid cycling experiences four or more (necessarily) brief episodes of mania, hypomania, or depression in a single year, with

good recovery between episodes. But psychopathology is rarely so tidy, and in the clinical setting one is often tempted to assign the rapid cycling specification to patients undergoing unpredictable mood changes with some mixture or alternation of symptoms of mania and depression. The DSM definition allows one to specify rapid cycling if the polarity switches include manic, depressive, or mixed states – but herein is a conundrum. If one understands mixed states to be a mixture or rapid alternation of manic and depressive symptoms, how can one identify a polarity switch? Or does the transition between manic and depressive symptoms within a mixed state make it *de facto* a form of rapid cycling (12)?

One solution to this conundrum is to look at mixed states as a special form of rapid cycling. In Kraepelin’s model, mixed states occur when separate components of affect (to paraphrase Kraepelin: mood, intellect, energy) begin to cycle separately, at different frequencies (Fig. 1A). Thus,

when all components are at a maximum, ‘classic’ mania results, and when all are at a minimum, melancholic depression. But a combination of, say, low mood with high energy and rapid rate of thought may be understood as a dysphoric mania, while the combination of low mood with sluggish thoughts (ruminations rather than flight of ideas) but excessive energy may be understood as agitated depression. If one were to accelerate these cycles (Fig. 1B), one can see that the result is a rapid succession of brief depressed and manic states with more prolonged periods of mixed symptoms. If the duration of each cycle is on the order of hours or less, one imagines a patient feeling quite buffeted by these chaotic moods and symptoms.

An alternative view of rapid cycling is to imagine these cycles entrained and cycling at the same rate, but at a faster pace than the typical case (Fig. 2). This model appears to be the assumption behind so-called ultra-rapid, or ultradian, cycling, in other words, changes in polarity occurring at frequencies

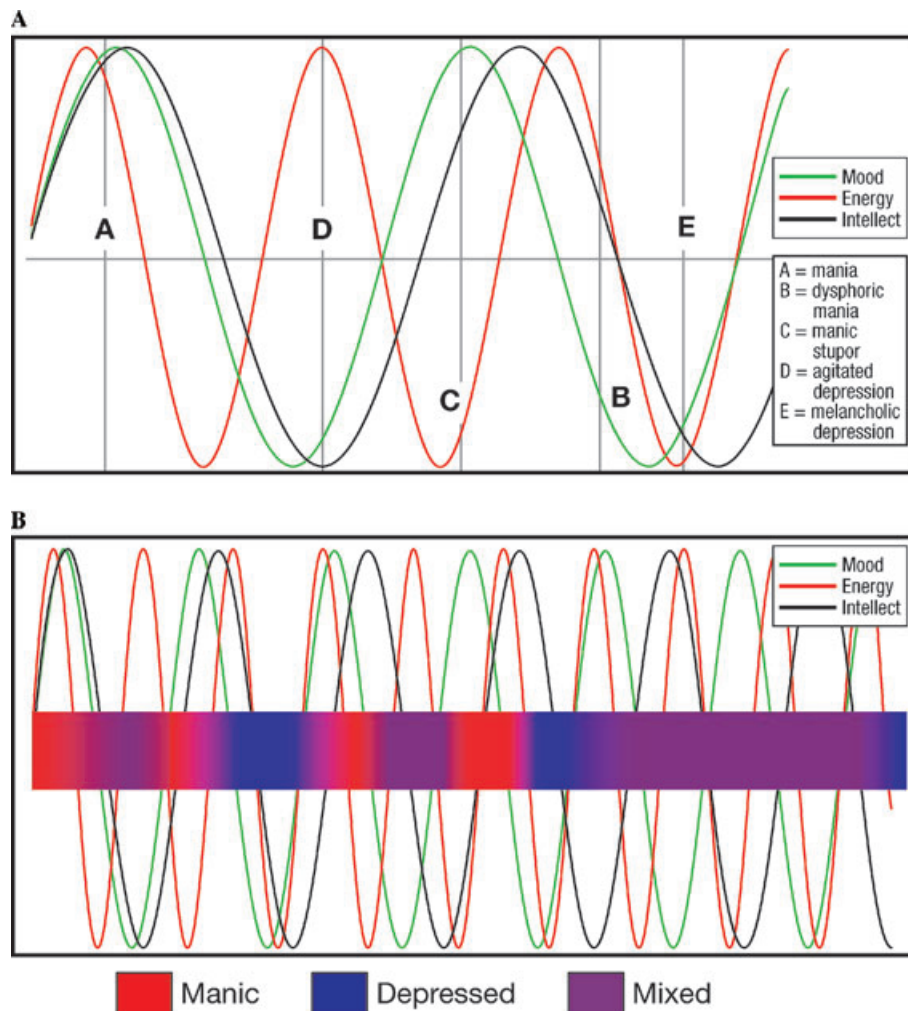


Fig. 1. (A, B) Kraepelin’s model of mixed states and an extrapolation of that model to the phenomenon of rapid cycling. Note that by the latter third of the diagram, symptom polarity is consistently out of sync, leading to a persistent mixed state.

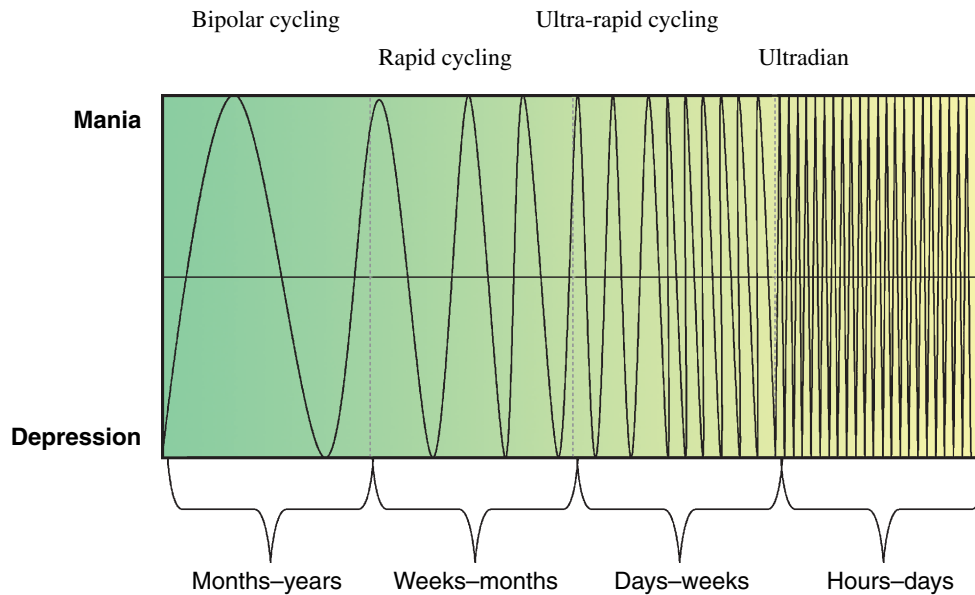


Fig. 2. Spectrum of bipolar disorder along an axis of increased frequency of episodes. If rapid cycling differs from 'classic' bipolar disorder by degree (rate of frequency) rather than form (quality of episodes), one might expect to see such an oscillatory pattern.

faster than once per 24 h (13). In such a patient one would expect to see discrete but brief episodes of pure mania or depression. However, at an extremely fast pace, the transition from one state to another might not register with the patient or clinician as something pure or predictable. Generally speaking, moods are not monitored continuously, but are assayed intermittently by the patient, by clinicians, and by emotionally challenging circumstances; measured at random, mood states following a pattern such as that illustrated in Fig. 2 might appear to be in a chaotic state of flux.

Whether one subscribes to the chaotic Kraepelinian model or sees extremely rapid cycling as a function purely of the rate of polarity change, the experience for patient and observer is one of unpredictable emotionality, fluctuating levels of activation from apathy to agitation, and unreliable cognitive powers. In some patients, these symptoms will manifest without any other behavioral evidence of personality disorder (13), while in others, the irascibility and destructive behavior that characterized an apparent personality disorder evaporate under antidepressant and mood-stabilizing medications. Although the 'affective instability' in the diagnostic criteria for borderline personality disorder is generally attributed to the borderline individual's marked interpersonal reactivity, in practice it is often hard to tell whether interpersonal problems trigger emotional reactions or whether the patient's unstable moods are the cause of the interpersonal problems (14).

There are compelling reasons for differentiating borderline personality disorder from bipolar disorder; foremost of which are the ways bipolar spectrum disorders and borderline personality disorder are different (15). In the absence of evidence about the similarity or differences in the mechanisms behind bipolar spectrum rapid cycling and borderline affective instability, there can be no definitive reason to commit to this position, as there are no definitive reasons to commit to the position that bipolar and borderline personality disorders are one and the same. The burden of proof is on the latter position, as the present nosology assigns them separate diagnoses, indeed, separate axes. In the absence of definitive knowledge, the decision to consider borderline personality disorder as akin to bipolar spectrum disorders is, in large part, a matter of utility.

How useful is the bipolar spectrum?

The notion of a 'spectrum' (or continuum) of bipolar disorders arguably dates back to the work of Kraepelin (1), who recognized the considerable quantitative and qualitative variability among patients with 'manic-depressive psychosis' (14). Uncertainty about the boundaries of the bipolar spectrum is reflected in the wide disparity in estimated prevalence rates. DSM-IV cites a lifetime prevalence of between 0.4% and 1.6% for bipolar I disorder, and a corresponding rate of about 0.5% for bipolar II disorder. Using a broader construct of bipolar disorder, Goodwin and Ghaemi (16)

estimated the prevalence of the 'broad spectrum' of bipolar disorder to be in the range of 2–5%, or about as common in their estimation as unipolar major depressive disorder (7). Using an even broader construct of bipolar disorder – one that includes 'temperamental instability along hypomanic or cyclothymic lines' – Akiskal arrived at the figure of 5–7% for the 'entire spectrum of bipolar disorders' (17).

The DSM has taken a conservative approach to the inclusion of disorders in the bipolar spectrum; bipolar II was introduced only in the latest edition, and with an arbitrary and perhaps overly stringent 4-day duration criterion for hypomanias (18–20). Although bipolar II can be diagnosed reliably using Research Diagnostic Criteria (21) for hypomania with duration as little as 2 days (22) and there is little doubt that it exists as a distinct clinical entity (18, 23), there is reason to believe that the diagnosis can be made reliably only by expert clinicians (24). This observation may be pertinent in comparing different approaches to diagnosis in the bipolar spectrum. The approach of Klerman, Akiskal, and others has been to split the spectrum into many sub-groups, based on specific characteristics; for example, depressed individuals with no history of hypomania/mania but with a 'cyclothymic temperament' – patients often considered to have borderline personality disorder – are classified by Akiskal as 'bipolar II ½' (20, 25). In contrast, Goodwin and Ghaemi (16) group all non-bipolar I and non-bipolar II sub-groups into one generic class of 'bipolar spectrum disorder.' Katzow (26) et al. put forth the concept of a 'smooth continuum,' ranging from mania on one end to depression on the other. Cycling can occur from any two points on this continuum, including '...cycling just within the depressive range.' This last point is extremely important, as it would include under the rubric of 'bipolar spectrum disorders' even those individuals who, in effect, cycle between 'somewhat depressed' and 'extremely depressed.' Indeed, these authors argue that the essence of bipolar illness may not be *cycling between mania and depression*, but rather, *any cycling at all*. By extension of this reasoning, a variety of 'impulsivity disorders' (including attention deficit hyperactivity disorder and borderline personality) are at least potential candidates for inclusion in the bipolar spectrum.

The problem with this expansive view of the boundaries of bipolar disorder is that the inclusion of all forms of affective instability under the rubric of bipolar disorder weakens the concept behind the diagnosis (27, 28). If the core concept of manic-depressive illness expands to include excessive

emotiveness and impulsivity, among other things, decades of research on patients with the 'classic' presentation may become inapplicable to patients who may have a more heterogeneous set of disorders. The concern is based on precedent. The history of the definition of schizophrenia, prior to the introduction of diagnostic criteria, saw expansion of the diagnosis to the point of meaninglessness (29). However, as Baldessarini acknowledges, 'further exploration of the limits and range of bipolar-like phenomena in psychopathology is an interesting and probably inevitable exercise, considering the limited bases for an objective and rational nosology' (28).

One might also argue that it is too late to close the door on acceptance of the bipolar spectrum, as the horse is already out of the barn; psychiatrists now routinely apply the bipolar diagnosis and prescribe anticonvulsants to a very broad range of patients. Because of this, there is growing recognition that the management of such patients is of great concern to public health (14). The question is whether it is more useful to lump all affectively unstable patients, including a subset of those with borderline personality disorder, under the same general category of bipolar spectrum disorders or to split them into fine categories based not only on symptom intensity and quality, but also on factors of behavior and circumstance. Experience with the bipolar II diagnosis suggests there may be diminishing diagnostic reliability with the addition of new diagnostic subtypes. If the aim is to see the overlapping symptoms of a variety of patients with affective instability as fundamentally the same sort of problem, it may be more useful to lump bipolar-like syndromes characterized by affective instability into a general class of bipolar spectrum disorder. In theory, breaking diagnoses into their phenomenological components moves one closer to the biological source of the problem (30). There is empirical evidence to support this change in perspective.

Links between borderline personality and rapid cycling bipolar disorder

I'm back to ultra rapid cycling. When I was sick at least I was consistently depressed. Now, that alternates with brief periods of manias that usually take the form of intense anxiety...
[<http://www.well.com/~jerod23/bp/UltraBlues.htm>]

Both borderline personality disorder and bipolar disorder can be diagnosed in the same patient, and often are. Higher than expected rates of

comorbidity may imply not only a relationship between two disorders, but that the two disorders are, at some level, one and the same (31). Several studies have demonstrated high rates of personality disorder among patients with bipolar disorder, with borderline the most common diagnosis (32, 33). Investigation into comorbidity between affective disorders and borderline personality disorder directly has supported these observations. One early study found that between 5% and 12% of borderline patients (using three sets of criteria) met DSM-III criteria for mania, whereas about 30% met criteria for depression (34). A recent study uncovered borderline personality disorder in 7% of patients with bipolar I and 12% of patients with major depression (35). In another recent study, the most frequent Axis II disorder seen in subjects with bipolar II disorder was borderline personality disorder; 12.5% of bipolar II patients met Research Diagnostic Criteria or DSM-III-R criteria for borderline personality disorder (36). The phenomenological overlap of affective instability and short-lived affective disorders has been noted directly with respect to 'ultra-rapid cycling' (13) and a proposed new diagnosis, 'recurrent brief depression' (37).

In addition to affective instability, there may also be overlap in the interpersonal 'maneuvers' used by borderline personality disorder and manic patients. Individuals in a manic state often attempt to manipulate the self-esteem of others; exploit areas of vulnerability; test interpersonal limits; and project responsibility or blame onto others, as is often the case with patients diagnosed with borderline personality disorder, with the common result of alienating the patient from significant others (38). In theory, the manic patient expresses such behavior only while in a manic state, whereas a patient with borderline personality disorder does so unremittingly.

The construct of 'affective instability' may require a more fine-grained understanding than has been provided to date. For example, are patients with this trait unstable across *all* affects, or only certain ones? These issues have been explored by Henry et al. (39) and Koenigsberg et al. (40) in complementary studies, using the Affective Lability Scale (ALS). This is a 54-item self-rating instrument that examines shifts into several affective domains – anger, depression, elation, and anxiety. Henry et al. (39) compared impulsivity and affective lability and intensity in patients with (i) borderline personality disorder alone, (ii) borderline personality disorder and comorbid bipolar II disorder, (iii) a personality disorder other than borderline (OPD) alone,

and (iv) OPD and comorbid bipolar II disorder. They found that, compared with bipolar II patients, patients with borderline personality had significantly higher total scores on the ALS. On ALS subscales, borderline patients displayed significantly more affective lability between *anger* and *euthymia*, whereas bipolar II patients displayed significantly more affective lability between *depression* and/or *elation* and *euthymia*. The authors concluded that both disorders share the trait of affective lability but have differing patterns of mood instability.

Using the ALS and the Affect Intensity Measure, Koenigsberg et al. (40) confirmed significant affective lability in a group of 42 patients with borderline personality disorder, in whom bipolar I disorder had been ruled out (40). Compared with *non*-borderline personality disorder subjects, the borderline subjects showed greater fluctuations into *anger* and *anxiety*, and oscillations between *depression* and *anxiety*. Among borderline subjects without a bipolar II diagnosis, there was no elation reported. Indeed, oscillation between *elation* and *depression* – as one might expect in classic bipolar disorder – was *not* significantly associated with borderline personality disorder. The authors concluded that careful attention to the type of affective oscillations might help distinguish borderline personality disorder from bipolar spectrum disorders. However, it is not always clear (as it was not clear to the patient quoted above) whether the anger and anxiety experienced by borderline patients are distinct in quality from the subjective mood experienced in an irritable or dysphoric *manic* state (41, 42). Thus, our interpretation of these complementary studies does not exclude the possibility that borderline and bipolar individuals share an underlying diathesis for extreme affective instability. It may be that an underlying genotype for such instability shows some phenotypic variance related to psychosocial factors that might differentiate borderline and bipolar individuals, for example, a higher likelihood of exposure to abusive environments or more unstable parenting in borderline patients. Further controlled studies examining such variables are needed to confirm this hypothesis.

Family studies

There are several lines of evidence from family studies supporting a possible genetic association of borderline personality and affective disorders. One analysis of the first-degree relatives of borderline probands found that 38% had a first-degree relative with depression and 25% had a relative with 'pathological mood swings' (43). Another

analysis, based on 100 probands diagnosed with borderline personality disorder found 17% to have at least one first-degree relative with bipolar disorder (44); in contrast, the rate of bipolar I and II disorder among first-degree relatives of probands with unipolar depressions was found in a large, multicenter study to be only 3.5% (45). Several similar analyses of the rates of affective disorder symptoms and syndromes among the relatives of borderline probands without affective disorder have found elevated rates of affective disorder, albeit not always specifically of bipolar disorder (46, 47). On the other hand, White et al. (48), in a review of the psychopathology found in relatives of borderline individuals, identified substance abuse and dependence disorders, as well as Cluster B personality disorders, as the most common conditions found in family members of borderline probands. However, the authors also point out that methodological limitations affecting many of these studies – such as the lack of direct evaluation of the majority of family members in all but one study – tend to introduce ambiguity into the interpretation of family studies of borderline personality. More salient to our argument, it is not clear that any of these studies differentiated the borderline syndrome with affective lability – which in our hypothesis may be a variant of bipolar disorder – from borderline personality without affective lability, which we do not maintain is a variant of bipolar disorder.

Genomic studies in bipolar spectrum and borderline personality disorders have been too few to be able to make meaningful contrasts or comparisons.

Neurobiological/anatomical studies

A number of studies suggest that some bipolar and borderline patients show overlapping functional and structural neuroanatomical abnormalities, especially involving temporal lobe and related limbic structures. Among a group of 14 adolescents and 22 adults with bipolar I disorder, compared with 56 healthy controls, an association was detected between bipolar disorder and decreased medial temporal lobe volume (49). The effects were greater in the amygdala than in the hippocampus. These abnormalities affected adolescent and adult subjects similarly, suggesting that brain structure may have been affected early in the course of illness. Similarly, several case reports suggest that damage to temporal lobe regions or surrounding structures may be followed by marked mood lability or rapid cycling. One such case involved a 48-year-old woman who developed rapid cycling

following traumatic brain injury to the left temporal pole; interestingly, her mood swings responded to coadministration of divalproex and lithium (50). Another case of ‘ultra-rapid cycling’ emerged in a young adult with no prior mood disorder history, following traumatic injury in the left frontotemporal region (51).

In a magnetic resonance imaging (MRI) study of 21 female patients with borderline personality disorder, there was a reduction in hippocampal volumes, and perhaps of the amygdala, compared with healthy controls (52). A follow-up functional MRI study by this same group, involving six borderline personality disorder patients with post-traumatic stress disorder (PTSD) and six without, showed areas of abnormal brain activation in both groups, although the PTSD group showed greater involvement of amygdala, anterior, and mesial temporal lobes (53). A separate MRI study of 10 borderline personality disorder subjects and 20 healthy controls found significantly smaller right and left hippocampal volumes among borderline subjects, most marked in subjects with a history of childhood abuse (54). A functional MRI study comparing six female borderline personality disorder patients with six age-matched female control subjects found evidence of elevated blood oxygenation in the amygdala bilaterally in borderline subjects, when viewing emotionally aversive (compared with emotionally neutral) slides (55).

Although intriguing overlaps are seen in the brain regions apparently affected by borderline personality and bipolar disorders, it is to be noted that there are no consistent findings in either disorder as yet that can definitively implicate a specific anatomic or functional lesion (56).

Pharmacologic studies in rapid cycling bipolar patients and borderline personality disorder

Studies of pharmacologic response can add an additional biological dimension to the comparison of two putatively related syndromes. Among the known effective treatments for rapid cycling bipolar disorder, anticonvulsants, as well as lithium to a lesser extent, are the only class studied systematically in both bipolar and borderline personality disorders, so these will be the focus of the discussion.

Rapid cycling patients

A review of treatment for rapid cycling bipolar disorder in the year 2000 described several challenges in the treatment of rapid cycling and

looked forward to ‘the development of a more systematic clinical trials literature to better use and sequence the combinations of pharmacotherapy so widely employed in the field’ (57). A more recent meta-analysis utilizing 16 clinical trial reports, 25 trial-arms, and 1856 patients (905 rapid cycling, 951 non-rapid cycling) examined treatment with carbamazepine, lamotrigine, lithium, topiramate, or divalproex, alone or with other agents, for an average of 47.5 months (7,347 total patient-years) (58). Pooled crude recurrence and non-improvement rates yielded no clear advantage for any treatment, or superiority for anticonvulsants over lithium. To our knowledge, there are only two randomized, double-blind, placebo-controlled studies of anticonvulsants in well-defined rapid cycling populations, both by the same group, and only one currently in the literature (59). In the published study, 182 rapid cycling patients were randomized to lamotrigine monotherapy or placebo. The study found that 41% of lamotrigine-treated versus 26% of placebo-treated patients were stable without relapse during 6 months of monotherapy. Patients with rapid cycling bipolar II disorder consistently experienced more improvement than did bipolar I patients. Most patients who were assigned to double-blind treatment were in the midst of a depressive episode, suggesting antidepressant effects of lamotrigine in bipolar disorder, consistent with the results of a separate, open-label trial of lamotrigine versus lithium in rapid cycling patients (60).

The second randomized, double-blind, controlled study (61) involved a 20-month, parallel group comparison of 60 patients with a history of recent rapid cycling bipolar I or II disorder. Patients were randomized to lithium or divalproex monotherapy in a balanced design after stratification for bipolar type I and II. For subjects on either lithium or divalproex, about half suffered a relapse: a third into depression, and one-fifth into mania or hypomania. Although clearly better than placebo, it appears there was no benefit of divalproex versus lithium.

Borderline personality disorder patients

Clinical trials of anticonvulsants in borderline personality disorder have been promising, if not always consistent. A controlled, 6-week, crossover study of carbamazepine, alprazolam, trifluoperazine, and tranylcypromine found that carbamazepine led to a reduction in physicians’ ratings of behavioral dyscontrol in 16 female patients with borderline personality disorder (62), although a

later double-blind, parallel, placebo-controlled trial of 20 borderline inpatients failed to show a significant effect (63). Several studies of divalproex have produced promising results. In an 8-week, open trial on 11 patients with borderline personality disorder, divalproex led to overall improvement in around half, in terms of mood and irritability, as well as for anxiety, anger, rejection sensitivity, and impulsivity (64).

Hollander et al. (65) conducted a double-blind trial of divalproex in 12 patients with borderline personality disorder, using a 10-week parallel design. Divalproex was more effective than placebo for global symptomatology, level of functioning, aggression, and depression. Specifically, there was a significant improvement from baseline in both global measures following divalproex treatment. However, a high dropout rate precluded finding significant differences between the treatment groups in the intent-to-treat analyses, although all results were in the predicted direction. In addition, the authors noted several limitations to this study due to small sample size, the imbalance in the number of patients in the two conditions, as well as an effect of the ‘inherent impulsivity and instability’ that lead patients with borderline personality to drop out of treatment studies at a high rate.

Frankenburg and Zanarini (66) performed a double-blind, placebo-controlled study of 30 patients carrying both bipolar II and borderline personality disorder diagnoses. Compared with placebo, divalproex significantly decreased irritability and anger, the ‘tempestuousness’ of patients’ relationships, and their impulsive aggressiveness. The study was limited by small sample size; bipolar II female subjects only; and subjects limited to ‘moderately ill’ outpatients who were not suffering concurrent major depressive episodes, abusing substances, or taking concurrent medications. The authors acknowledged that their results might not be applicable to a more severely impaired patient group. It is notable, however, that two separate trials of divalproex in mixed samples of personality-disordered patients similarly showed a significant effect of divalproex against measures of aggressiveness (67, 68).

Preliminary data suggest that lamotrigine may also have benefits in borderline personality disorder, with or without comorbid bipolar disorder. In an open case series of eight medication-refractory borderline personality disorder patients without concurrent major mood disorders, lamotrigine produced sustained remission in half of those who completed the trial, with

notable benefit against impulsive sexual, drug-taking, and suicidal behaviors (69). Three of these eight subjects had a positive family history of bipolar disorder. In a separate study of the efficacy of lamotrigine in 35 patients with bipolar disorder, the 14 patients who also met criteria for borderline personality disorder all experienced affective instability as a symptom of their personality disorder and, as a group, showed significant improvement across this as well as all other specific dimensions associated with borderline personality disorder (70). Randomized, double-blind, controlled studies using lamotrigine appear warranted in this population; however, until these are completed, the utility of lamotrigine in borderline patients remains uncertain.

Nevertheless, one can conclude from the juxtaposition of these studies of anticonvulsants in rapid cycling bipolar disorder and borderline personality disorder that at least some anticonvulsants are effective in alleviating not only the affective instability common to both conditions, but also specific measures of what have heretofore been considered fixed traits among borderline patients. Anticonvulsants such as lamotrigine may have a number of potential points of influence on brain functioning – suppression of the rapid firing of neuronal action potentials via inhibition of glutamate release, or inhibition of specific subtypes of voltage-gated calcium channels, or inhibition of sodium channel activity in a voltage-dependent manner, as well as other non-glutamate neurotransmitter effects – and any or all of these might be the mechanism of therapeutic action in borderline and bipolar disorders (71). Intriguingly, both borderline personality disorder and bipolar disorder may also place patients at adverse risk of developing increased agitation under the influence of antidepressant therapy (72). Similar clinical responsiveness to treatment does not prove similarity of pathophysiology; however, it does provide an additional reason not to rule out the possibility that the affective instability seen in borderline personality disorder and that in bipolar spectrum disorders derive from the same mechanism.

Nonetheless, distinguishing *affective instability* from the *impulsivity* often seen in these two conditions remains a challenge. It is very difficult, in retrospect, to ‘reconstruct’ a patient’s affective state at the time of a specific impulsive behavior, or to link a particular affective shift to a particular impulsive behavior. This same conundrum also makes it difficult to tease out medication effects on affective instability *per se*, versus effects on behavioral impulsivity.

A model for the development of borderline personality disorder on the basis of unstable mood states

If the evidence presented thus far provides sufficient support not to reject the hypothesis that borderline personality disorder (when it involves affective instability) belongs in the broad spectrum of bipolar disorder, the question remains how to account for the differences between borderline and (at least in the rapid cycling or mixed form) bipolar disorders. Assuming they start at a common point, where and how do they diverge? One can construct a plausible heuristic model based on the supposition that what is ultimately diagnosed as ‘borderline personality disorder’ arises, in many cases, from a primary, neurodevelopmental tendency toward mood instability. Under this model, a ‘vicious circle’ arises from the synergistic interaction of a primary mood disorder with environmental factors that exacerbate, rather than accommodate, the patient’s affective instability. If one posits that such toxic interactions begin with the earliest relationships, it follows that psychodynamic and object-relational models of borderline personality disorder – as well as models based on the role of trauma – are fully compatible with this schema (Fig. 3; circled numbers in figure are linked with text points 1–8, immediately below).

To state the model as well in words, the sequence might proceed as follows:

- 1 An underlying structural and/or functional brain abnormality – perhaps rooted in genetics and affecting temporo-limbic regions – predisposes the developing child to unstable mood states.
- 2 The child receives inconsistent nurturing, rewards, and punishments. This may arise in part because of a primary impairment in the child’s ability to perceive rewards and punishments (the result of the mood instability), and in part because the child’s mood instability contributes in some cases to the development of inconsistent or even abusive parenting styles from frustrated caregivers – even more of a risk if the parent also has unstable moods.
- 3 The inability to perceive consistent reward or to learn from consequences becomes a source of stress directly, as the child struggles to learn what is expected, while at the same time the failure to learn from consequences or to behave consistently creates tension and impaired bonding with the primary parent or mothering figure.
- 4 During critical developmental periods, such as the ‘separation-individuation’ phase at 18–36 months, impaired infant–parent bonding

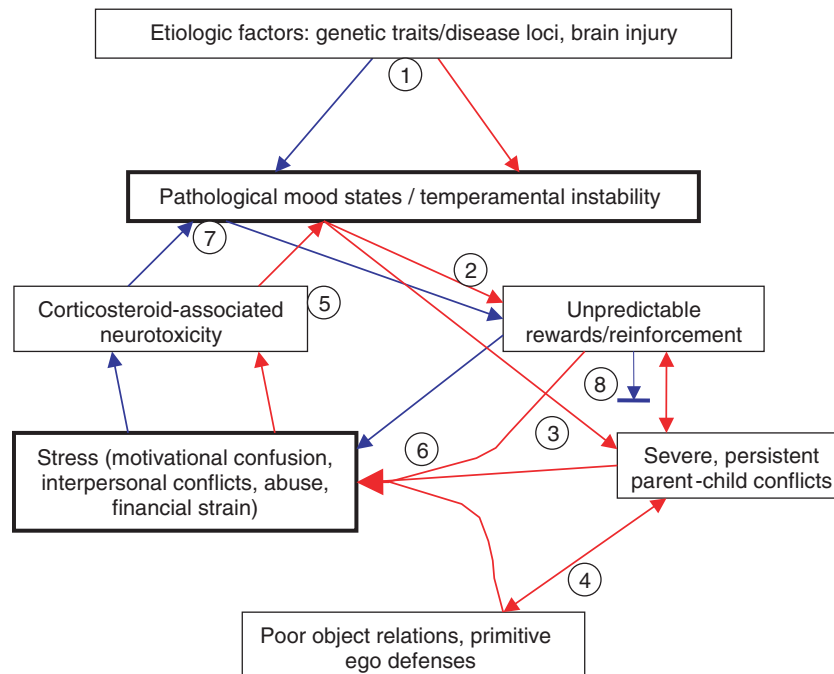


Fig. 3. A descriptive model of the interrelationship of mood and personality disorder (circled numerals are linked to discussion in main text).

(i) Both the vulnerability to unstable mood states (e.g., rapid cycling bipolar disorder) and to unstable temperaments may derive from genetics or other insult to the optimal emotional functioning of the brain.

(ii) *Red arrows* illustrate the 'vicious cycle' by which the combination of temperamental vulnerability and unsupportive environment can lead to frank affective symptomatology. Pathological or inappropriate affective states affect reward/punishment perception directly, and also in a reciprocal way, by leading to a cycle of conduct problems and inconsistent parenting. Severely and persistently conflicted relationship with parents adversely influences psychological development. All of these factors produce stress, which affects brain systems involved in mood regulation. The cumulative effect of this cycle is more mood dysregulation and worsening problems with conduct, relationships, and psychological integrity. Such patients may sometimes come to be diagnosed with 'borderline personality disorder.'

(iii) *Blue arrows* illustrate a typical, relatively uncomplicated case of familial bipolar disorder. The patient experiences a cycle from temperamental vulnerability to life problems, influenced by impairment in reward perception, leading to stressful situations, with the resulting harmful effects of stress on brain functions involved with maintenance of affective stability. However, in the context of relatively mild parent-child difficulties (the blocked blue arrow), the second loop of the cycle is avoided, and the patient 'escapes' personality disorder. Factors that would block the cycle through parent-child conflicts might include high parental resiliency and resourcefulness; prolonged periods of relative affective calm when healthy psychological development can proceed; and complementary features of temperament in the child (e.g., conscientiousness, stoicism) to counteract affectively driven behavior.

leads to faulty internalization of a safe, reliable, parental 'object.' The child begins to develop primitive ego defenses, such as splitting and projection, to deal with the resulting dysphoric feelings (73). The behavioral impact of these defenses on others may further strain relations within the family and may also produce constant stress.

5 The neuroendocrinological response to the chronic stress produced by 2, 3, and 4 has deleterious effects on limbic and mesiotemporal structures (74, 75). These effects, in turn, serve to exacerbate the congenital trait toward affective instability and may contribute to the development of frank affective disorder symptomatology (76). The amount of stress required to produce a frank affective disorder is probably inversely proportional to the degree of familial risk in a given individual (77).

6 The cycle continues outside of the home, as the child's inherent mood instability and use of pathologic defenses foster poor interpersonal relationships with peers, teachers, and others. Either at home or in other settings, the individual may be physically abused or enter into abusive relationships. Lack of consistent experiential pairing of positive acts with rewards (e.g., friendships, academic success) or of destructive acts with punishments (remorselessness derived from manic self-confidence or, alternatively, an inability to perceive punishments against a background of depressive self-loathing) leads to the perpetuation of self-destructive behavior patterns.

7 Repeated experiences of abuse, trauma, and self-injurious behavior lead to enduring changes in brain reactivity or 'sensitization' of neural tissue, primarily affecting (already abnormal)

temporal and limbic regions. These changes may be mediated, in part, by abnormal hypothalamic-pituitary-adrenal function (78). Enhanced amygdala activation (55) may lead to further mood instability, thus perpetuating the 'borderline' cycle. Treatment with lithium or anticonvulsants may offer neuroprotective effects against such deleterious changes (79).

- 8 In contrast, a person born with a trait toward affective instability who grows up in an adequately nurturing environment (or who has other compensatory assets) becomes adept at reading behavioral cues and consequences, and thus endures less profound, if any, significant disturbance in parental bonding or object relations. If this person goes on to develop a problem with pathological mood instability, it is more likely to take the form of an 'ultra-rapid cycling' bipolar syndrome with healthy functioning and relationships when episodes are controlled.

This model, while heuristic and conjectural, has empirical support for several key components. An analysis of the relative roles of childhood abuse and affective lability in the development of personality disorders found evidence for a limited role of emotional abuse in the etiology of borderline personality disorder and suggested that 'non-childhood variables, such as an inherited affective instability trait, may be more important in the etiology of affective dyscontrol' in borderline personality (80). It has been observed by at least one investigator that childhood bipolar disorder tends to present with affective instability, not with discrete episodes of mania and depression (81). Affective instability in patients with borderline personality disorder is significantly correlated with the identity disturbance, chronic emptiness or boredom, and suicidality, as well as with 'primitive' ego defenses, such as splitting, projection, and acting out (82). The traumatic experiences often associated with such psychological vulnerabilities have been found to produce alterations in brain structure and function (75, 83). Moreover, there are reasons to believe the development of constitutive mood instability as a function of stress may take place over many years (84). It should be noted that this model probably applies more closely to rapid cycling or mixed forms of bipolar disorder than to non-rapid cycling forms. One essential element of the model is that mood states in affected individuals start out as chaotic and unpredictable, thus increasing the potential for maladaptive interactions with the environment. Gradual onset and persistent depressive and manic mood states,

while destructive in their own ways, are probably more likely by patients and family members to be seen as pathological states, rather than as maladaptive emotional responses.

The utility of this model may prove to be the insight that psychological and somatic interventions may be aimed at 'breaking the cycle' of borderline personality disorder development at various points. It also illustrates that if one views the affective instability in borderline personality and that in bipolar spectrum disorders as expressions of a common mechanism (85), there is theoretical support to trials of mood-stabilizing anticonvulsants in borderline personality disorder.

Conclusions and implications for treatment

A mixed pattern of reports supporting or failing to support the hypothesis that borderline personality disorder is a form of bipolar spectrum disorder is explainable by the methodological limitations of biological research into psychiatric disorders and, perhaps more importantly, by heterogeneity within the diagnostic boundaries of each sort of disorder. It is possible to have a diagnosis of borderline personality disorder and not have the symptom of affective instability; one might predict such patients would appear less similar to bipolar spectrum disorder patients than would patients with affectively unstable borderline personality. It is possible to have extremely rapid shifts in mood symptoms and yet not exhibit the behavioral difficulties that characterize borderline personality disorder. The conclusion drawn from the studies reviewed in this paper is that affective instability – or, in less theoretically biased terms, rapid switching of mood – may be a highly productive endophenotype toward the understanding of mood regulation and its disorders. Rapid mood switching, as detected in a large collaborative family study of bipolar disorder, is a common symptom experienced by over 40% of individuals with bipolar disorder and is associated with early age of onset of bipolar disorder, higher risk of anxiety and substance abuse, and suicide attempts (86).

One clinical implication of this review is to offer theoretical and biological support to the ongoing clinical investigation of the use of anticonvulsants and other anti-manic treatments in some forms of borderline personality disorder. Although bipolar and borderline patients are clearly distinct in important ways, the same mechanism may drive both the rapid mood switching of bipolar disorder and the affective instability of borderline personality disorder, and may even be rooted in the same

genetic etiology. One would predict that anticonvulsants and other treatments useful in rapid cycling bipolar disorder would be selectively beneficial in borderline patients manifesting affective instability.

A potentially important research implication of this review is to reiterate the view that investigations into bipolar disorder might prosper by taking into account phenomena that are not captured in the diagnostic criteria by which research subjects are typically categorized. The phenomenon of rapid mood switching, whether it appears as a feature of a diagnosed bipolar illness or in the context of borderline personality disorder, might prove a useful marker in one of two ways. If one hypothesizes that such subthreshold phenomena denote an extended phenotype of the core disorder, then one can expand the population of potentially informative subjects, in the way schizotypal and schizoid personality disorders have been useful in investigations into the causes of schizophrenia (87) and pervasive developmental disorders have been used in autism (88). Alternatively, if one considers rapid switching to be an alternative form of bipolar disorder, possibly independent of the causes of 'classic' bipolar disorder, then it might be useful to consider rapid switching individuals as constituting a separate type, and to thus account for the heterogeneity they might introduce into investigational diagnostic groups.

It is not our aim to take sides in the debate over the expansion or restriction of the bipolar diagnosis with respect to a spectrum of bipolar-like disorders. We believe this review establishes that the overlap of symptoms between an Axis I and an Axis II disorder generates many potentially fruitful questions about the nature of mood disorders, the genesis of personality disorders, and the management of both. As the answers to these questions begin to take shape, it seems likely that the imprecise categorical approaches reflected in the currently confusing rubric of 'rapid cycling,' 'ultradian cycling,' 'affective lability,' etc., may give way to an understanding of affective instability as a dimensional problem related to the rapidity of change of mood and related affective symptoms. Once the biological roots of mood instability are better understood, there may be much more to contribute to the understanding of the development of our conventional notions of character and personality.

We conclude that in at least a sub-group of cases, borderline personality disorder may be an atypical presentation of a primary mood disturbance, probably related to the broad spectrum of bipolar-like disorders. It is premature to recom-

mend anticonvulsants in the routine treatment of patients with borderline personality disorder; however, it seems that anticonvulsants may belong in the psychiatrist's armamentarium for treatment of this condition. Further research should clarify whether anticonvulsants, perhaps combined with appropriate psychotherapy, may help to break up the 'vicious cycle' of mood instability and impaired interpersonal relations that characterize borderline personality disorder.

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