Recent suggestions to extend the boundaries of bipolar disorder to a broader spectrum lead to a concept of bipolarity different from that of classical psychiatry. It has been proposed that many patients with unipolar depression are actually bipolar and that many cases of substance abuse, personality disorders, and childhood behavioral disorders lie within the spectrum. However, since this expanded notion of bipolarity has been defined entirely on the basis of phenomenology, any expansion needs to meet broader criteria for validity. Bipolar spectrum disorders have a different phenomenology, family history, and course than classical bipolar disorders and do not respond in the same way to drugs. Until further research clarifies the boundaries of bipolarity, we should be conservative about extending its scope. (Harv Rev Psychiatry 2009;17:206–213.)

Keywords: bipolar disorders, bipolar spectrum, mood disorders

Recent suggestions to extend the boundaries of bipolar disorder—to include a broader spectrum—lead to a concept of bipolarity different from that of classical psychiatry. In particular, it has been proposed that many patients with unipolar depression are actually bipolar and that many cases of substance abuse, personality disorders, and childhood behavioral disorders lie within the spectrum. In this review, the proposed bipolar spectrum will be critically examined in terms of existing psychiatric knowledge and the possible justifications for expanding existing disease categories to include a broader range of phenomena.

This review was prepared by searching Medline for all articles since 1987 concerning bipolar spectrum disorders. That strategy identified 262 articles, which are the main focus of the current review. An additional search was also conducted for articles within the same period, identifying 441 articles on unipolar depression and bipolar disorder, 398 on substance abuse and bipolar disorder, and 685 on personality disorder and bipolar disorder. The references cited in this article are either systematic reviews or reports of key research findings that shed light on the validity of the bipolar spectrum.

**Diagnostic Validity and Diagnostic Boundaries**

Classification has always been a problem in psychiatry, largely because the diagnosis of mental disorders has only rarely been based on an understanding of etiology and pathophysiology. Instead, current categories are mainly defined by phenomenology. In medicine, similar symptoms can derive from entirely different causes. Features based on observation alone may be no more specific than fever or inflammation. Clinical symptoms are subject to differential diagnosis, however, assisted by precise and specific laboratory tests. In the absence of knowledge about etiology and pathophysiology—and, most particularly, without biological markers—clusters of signs and symptoms tend to organize only into syndromes, not diseases.

At present the causes of most mental disorders are unknown. Kraepelin accepted phenomenologically based diagnosis as an interim measure to be used until physical
the inevitable artifact of a system that applies few exclusions.

For the major conditions that psychiatrists treat, no laboratory tests or imaging findings are available to guide diagnosis. That is why the latest version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) used the term “mental disorder,” as opposed to “mental illness” or “disease.” In the absence of etiological data, few DSM disorders—even massively researched categories such as schizophrenia, melancholic depression, and bipolar disorder—can yet be considered to have the status of diseases. Most diagnoses are syndromal, describing clusters of signs and symptoms that may or may not have a common etiology. The result has been massive “comorbidity”—the inevitable artifact of a system that applies few exclusions.

Robins and Guze developed the most influential criteria for diagnostic validity in psychiatry: (1) clear-cut clinical description, (2) laboratory studies, (3) delimitation from other disorders, (4) follow-up studies documenting a characteristic outcome, and (5) family prevalence studies. While the DSM system did attempt to provide clear-cut descriptions, it did not always succeed, and the other criteria are rarely met. Laboratory findings, the backbone of diagnosis in internal medicine, have not been consistent enough to distinguish between diagnoses. And unlike other specialties, imaging in psychiatry has not yet been useful for resolving problems in differential diagnosis. The extensive comorbidity in the DSM system shows it to be weak on the criterion of delimitation. A century ago, Kraepelin emphasized outcome as a criterion—for example, in separating schizophrenia from bipolar disorder—but the distinctions between these conditions still remain unclear. Family prevalence studies also find great overlap between disorders.

Diagnostic categories can become popular for reasons other than their validity. In the history of medicine, diagnoses have often been made more frequently when new methods of treatment appear. The appearance of effective therapeutic agents makes clinicians want to use them for refractory patients—a practice that can be justified by redefining clinical problems as lying within an existing disease category or spectrum.

Psychiatry has seen several examples of this scenario. Fifty years ago, diagnoses of ambulatory or “pseudoneurotic” schizophrenia, influenced by the success of neuroleptic therapy, were common. Bipolar disorder, given the striking response of classical cases to pharmacological therapy, is currently undergoing a similar evolution.

The usefulness of lithium for acute treatment of mania and for prevention of relapses has been demonstrated in many studies. These data led psychiatrists to reconsider whether patients falling in other categories might actually suffer from bipolar disorder.

Other categories of psychosis were the first target for re-diagnosis. Abnormal states of excitement previously categorized as catatonic schizophrenia were thus redefined as forms of mania. “First-rank” symptoms of schizophrenia—such as thought broadcasting and thought insertion, long considered to be pathognomonic of schizophrenia—were found to be common in manic patients. The most convincing evidence for changes in diagnosis was that some patients previously diagnosed with schizophrenia could be treated successfully with lithium. However, pharmacological response, by itself, cannot establish valid diagnostic boundaries.

The concept of a bipolar spectrum began with Kraepelin, who suggested that milder forms of mania can exist in the absence of classical symptoms, sometimes presenting only as “characterological” features. The category of cyclothymic disorder describes some of these subclinical cases, but this diagnosis is not often used, in part because of its heterogeneity.

The diagnosis of bipolar II disorder, which describes mood swings from depression to hypomania, has been much more influential. Yet patients meeting criteria for bipolar II can also be heterogeneous. Only some have a family history of bipolar disorder—which, when present, tends to be associated with better pharmacological responses. Also, mood stabilizers in bipolar II produce less consistent effects than in bipolar I, whereas patients with characterological disturbances that cloud the clinical picture do not respond as well to medication.

In the last decade, a proposal for a widened bipolar spectrum has been widely discussed. The construct would be greatly expanded, beyond bipolar I and bipolar II, to describe a wider range of conditions previously categorized in other ways. Bipolarity would 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. While induction of hypomania by antidepressants is a well-established phenomenon, the proposal to create a bipolar IV category remains controversial. It has also been suggested that a range of other disorders show symptoms of bipolarity that place them in the spectrum and that subthreshold symptoms are common in nonpatients.

A wider bipolar spectrum would have a much higher prevalence than classical manic-depression. Epidemiological research has been reported increasing levels of lifetime prevalence over time, even for existing categories. In the Epidemiological Catchment Area study, bipolar I was 0.8%,
and bipolar-II 0.5%.27 In the National Comorbidity Study, the lifetime prevalence of manic episodes was 1.6%.28 The National Comorbidity Study Replication reported a combined prevalence for bipolar I and bipolar II as 3.9%.29 A second report from NCS-R, which was designed to determine the frequency of bipolar spectrum disorders, found that bipolar I had a prevalence of 1% and bipolar II of 1.1%,30 while subthreshold cases assessed with a new instrument added an additional 2.4%.31 And estimates based on an even broader concept of the spectrum have come in as high as 6%32,33 in one report total lifetime prevalence was estimated as over 8%.34 In clinical samples, in which protocols designed to identify spectrum symptoms are used, prevalence can be even more dramatically elevated: 39% of all patients in a large study of patients at multiple sites in France were found to have had episodes of broadly defined hypomania.35

The problem with this research is the absence of a gold standard for a diagnosis of bipolarity. Epidemiological or clinical studies to examine the prevalence of spectrum disorders either use scales designed to assess symptoms of “soft bipolarity,”36 or identify spectrum cases through the presence of subthreshold symptoms using the diagnostic measures of the DSM or International Classification of Diseases.31 But these conclusions are based on prior assumptions that subthreshold symptoms are indicators of bipolarity. Phenomenological resemblances are not sufficient, however, to determine whether the spectrum concept is valid.

An alternative point of view is that subclinical symptoms of moodiness can reflect either a different phenomenon or normal variations that are not necessarily related to classically defined mood disorders. A parallel problem exists in determining the boundaries between severe depression (in which symptoms are not accounted for by stressors) and normal sadness after a loss.1 Even if mental disorders and normal reactions to life events share certain symptoms, they may not be derived from a single pathological mechanism.

MANIA, HYPOMANIA, AND AFFECTIVE INSTABILITY

Mania has always been defined in relation to a classical triad of symptoms: elevated affect, psychomotor excitement, and racing thoughts.9 Classically, psychiatrists have not diagnosed mania in the absence of euphoria. However, after the introduction of lithium, it was observed that bipolar I patients can show irritability (rather than elevated mood) and that this symptom can respond to mood stabilizers.10 That observation led to questions as to whether states of excitement, irritability, and aggression seen in other categories of mental disorder are symptoms of mania and whether the classical triad is a necessary condition for bipolarity.

Manic and hypomanic episodes also have requirements defined by time scale and persistence. The key issue in making a bipolar II diagnosis lies in ensuring that patients meet criteria for hypomania. A hypomanic episode, as defined in DSM-IV-TR,3 consists of “persistently elevated, expansive, or irritable mood, lasting throughout at least 4 days.” If not directly observed, the assessment of hypomania by retrospective patient report is difficult since one cannot readily determine whether mood elevation was persistent or how long it lasted.37 When patients describe brief periods of elevated mood that do not persist, these episodes may not correspond to hypomania.

It has been suggested that if hypomania is a dimension, the presence of symptoms for the full four days should not be required.38,39 But such a change begs the question as to whether brief changes in mood are actually related to bipolar disorder. Another proposal is to narrow down the definition of bipolar II by requiring that any depressive episodes fulfill criteria for melancholia and by also requiring that hypomanic episodes be marked by an absence of anxiety.39 But the broader question is whether, before introducing a spectrum concept that would lead to major changes in psychiatric diagnosis, we should determine if mood swings share a common psychopathological mechanism.

The problem of defining boundaries is even greater with ultra-rapid mood swings, proposed to characterize bipolar IV disorder. But while rapid-cycling bipolar illness has been studied,40 we do not know whether “ultra-rapid cycling,” in which mood changes from day to day or even hour to hour, is actually a form of mania. While these symptoms are pathological, they could be based on a different mechanism.

The main alternative to seeing all mood swings as bipolar phenomena is the construct of affective instability (AI),41 also called emotion dysregulation.42 This term describes brief mood changes characterized by temporal instability, high intensity, and delayed recovery from dysphoric states. The construct points to a distinction between environmentally driven, short-duration mood swings (AI) vs. spontaneous, long-duration mood swings (bipolar and unipolar mood disorders). Although research on AI is still in its early stages, it describes phenomena seen in patients with a wide range of mental disorders.41 AI can be reliably measured and separated from mood intensity, is distinct from both affective intensity and neuroticism,43 and has been show to be a heritable trait.44

DISORDERS PROPOSED TO LIE IN A WIDER BIPOLAR SPECTRUM

The most important implication of an expansion of bipolarity would be to view other mental disorders as falling within the same spectrum and as benefiting from similar
treatment. Three groups have been widely discussed in the literature: unipolar depression, adult impulsive disorders (substance abuse, bulimia, and Cluster B personality disorders), as well as childhood behavioral disorders.

Unipolar Depression

Kraepelin\(^2\) was the first to suggest that recurrent unipolar depression can develop over time into bipolar disorder. Several lines of evidence support this hypothesis. First, when unipolar depression has an early onset, a recurrent course, atypical symptomatology, or irritability and hostility, it may go on to present with manic or hypomanic episodes or be associated with family histories of bipolarity.\(^5\) Second, some patients with unipolar depression and family histories of bipolarity show rapid shifts in mood.\(^48\) Third, mood stabilizers such as lithium are useful adjunctive agents for some cases of treatment-resistant depression.\(^9\),\(^49\)

This relationship could be even stronger if one applied a broader concept of bipolarity. It has been suggested that that up to 77% of all patients with recurrent unipolar depression meet “soft” criteria for bipolar disorder.\(^50\) This concept has led to the suggestion that unrecognized bipolarity could be a major cause of treatment-resistant depression.\(^51\)

The relationship between unipolar depression and bipolar disorder may be exaggerated, however, by applying spectrum concepts. For example, while family history can be helpful, it can be difficult to make these distinctions in practice. One study that applied a large number of risk factors found it difficult to find any distinctions between unipolar patients who had unipolar relatives from those who had bipolar relatives.\(^52\)

Impulsive Disorders

Since impulsivity can be associated with mania or hypomania, it has been suggested that this behavioral pattern might reflect another form of bipolarity. On this view, impulsivity would be secondary to mood instability, rather than considered as a separate domain.

Specifically, it has been suggested that many patients with a primary diagnosis of substance abuse could have an underlying bipolar disorder,\(^24\),\(^53\) given that substance abuse can produce clinical symptoms such as euphoria and irritability, as well as psychomotor excitement and abnormalities of thought.\(^54\) Similar proposals have been made concerning the relationship of binge-eating disorder and bulimia nervosa to bipolarity.\(^55\)

The issue is whether the emotional dysregulation associated with impulsive disorders reflects bipolarity or some other mechanism. Substance abuse is known to run in families, and although it is frequently comorbid with bipolar disorders, family studies have not found any strong association with classically defined bipolarity.\(^56\) Also, impulsive disorders tend to “burn out” with time,\(^57\)–\(^59\) a pattern not seen in bipolar disorders.\(^60\),\(^61\)

Personality disorders, particularly those in Cluster B of Axis II, which can have prominent impulsive symptoms (often associated with mood instability), have also been hypothesized to represent a form of bipolarity.\(^62\) But in patients diagnosed with borderline personality disorder, rapid shifts in mood are qualitatively different from those seen in bipolar II disorder;\(^63\),\(^64\) euphoria is rare, and most swings go from depression to anger. Moreover, the affective instability that characterizes patients with this diagnosis is highly sensitive to environmental cues and interpersonal stressors.\(^65\)

Finally, family studies of patients with borderline personality disorder suggest that diagnoses reflecting impulsivity—such as substance abuse and antisocial personality, but not bipolar disorders—tend to “breed true.”\(^66\)

Childhood Behavioral Disorders

Since the time of Kraepelin,\(^2\) it has been generally believed that mania begins no earlier than adolescence. Recently, the proposal that mania can begin in childhood\(^67\)–\(^69\) (prior to puberty), when it may present only with irritability and behavioral symptoms, has gained wide influence. The argument for the existence of childhood bipolarity is based on a phenomenological resemblance between phenomena seen in adult bipolar disorders and the clinical picture of aggressive behavior and emotional dysregulation in children. In the past, clinicians have categorized most behavioral problems in childhood using diagnoses of conduct disorder, oppositional defiant disorder, and attention-deficit/hyperactivity disorder, and have not seen mood instability as primary.

Based on current diagnostic practices, large-scale epidemiological studies do not identify cases of bipolarity before puberty.\(^70\) Although it might be argued that such cases are going unnoticed, it has never been shown that children with this clinical picture go on to develop bipolar disorder in adulthood. Thus far, follow-up studies have lasted only for a few years,\(^71\),\(^72\) and what they show is that while cohorts remain symptomatic, symptoms do not evolve into either mania or hypomania.\(^73\)

The question is whether irritability and impulsivity in children and adolescents are really indications of bipolarity. Community surveys suggest that these symptoms are widely distributed in the general population.\(^74\),\(^75\) One cannot conduct valid epidemiological studies based on these criteria unless they can be independently validated. And the hypothesized relationship of these phenotypes to bipolarity has not been supported by the identification of common markers.
VALIDATING THE BIPOLAR SPECTRUM

Let us now examine the validity of the bipolar spectrum by applying the criteria of Robins and Guze.5

Concerning clear-cut clinical description and delimitation from other diagnoses, the spectrum concept assumes that mood swings, however brief, as well as impulsivity and irritability, are bipolar phenomena. As we have seen, this conclusion is open to question. Laboratory studies and biological markers are virtually absent from this literature. Course and outcome, based on large-scale longitudinal data, have been conducted on classical bipolar disorder61 but not on spectrum disorders. Family prevalence data are, at best, mixed, and there is even a suggestion that bipolar II might be genetically distinct.76

But there are other ways to validate diagnostic constructs. If one could identify a common genetic factor shared by spectrum disorders and adult bipolarity,77 the construct would gain strong support. But at this point, genetic association and linkage studies have identified genetic markers that overlap schizophrenia and mood disorders.78−80

Still another strategy involves validating diagnoses by identifying a characteristic treatment response. “Pharmacological dissection” is based on showing that the same agent produces the same effect in patients falling in different categories. But while bipolar disorder usually responds to mood stabilizers, there is an absence of randomized clinical trials for these drugs in spectrum disorders. Thus, while lithium is known to have an adjunctive role in depression, mood stabilizers have not been tested in RCTs in substance abuse81 or in eating disorders,85 whereas impulsive personality disorders82 and conduct disorder83 respond only partially to these agents, without the full remissions that one might expect in bipolar I or bipolar II.

Pharmacological dissection is limited by the fact that psychiatric drugs have a broad spectrum of effects. The partial responses seen in putative spectrum conditions are consistent with that principle. Similarly, while antidepressants are effective for anxiety disorders, and neuroleptics have been used to control impulsivity, these responses do not prove that one is dealing with common endophenotypes. No one would claim that relief from pain obtained by prescribing analgesics proves that all patients with such a response have the same pathophysiology.

Comparing psychiatry to internal medicine, the absence of biological markers and laboratory data again emerges as a key problem. When that kind of data became available to internists, physicians learned that diseases such as lupus erythematosus and syphilis can produce widely different symptoms, and that syndromes like jaundice can derive from widely different disease processes.

FUTURE RESEARCH AND CLINICAL IMPLICATIONS

One overriding aim of the bipolar spectrum is to describe a common etiological mechanism behind many categories of disease. Yet at present we do not even understand the causes of bipolar I disorder. Again, the key problem is an absence of biological markers. As in the rest of medicine, the identification of diseases, as opposed to syndromes, must depend on objective measures that transcend phenomenological observation. Thus far, neuroscience research has not even been able to solve critical problems in psychiatry, such as whether Kraepelinian distinctions are valid.6

At this point genetic associations have not been found that are specific to mania, nor has it been linked by imaging research to specific brain regions or to specific changes in neurotransmitter activity.9,84 Perhaps researchers should focus on finding a more precise definition of classical bipolarity before extending the concept to other clinical presentations.

Without biological markers, identifying what is and is not bipolarity remains uncertain, and we run a serious danger of overdiagnosis.85 Defining large numbers of patients as having a single, highly prevalent illness might be called “bipolar imperialism,” and it assumes too much from a limited data base.

The debate over the boundaries of bipolar disorder is far from academic. Expansion of the bipolar spectrum would have vast implications for treatment. Findings of subclinical cases in the community could be interpreted as being true cases that require active treatment, but they could also be normal variants that do not require medical intervention. In the latter case, an inflated prevalence would lead to the prescription of drugs to patients who would not actually benefit from them.

If drugs such as mood stabilizers and neuroleptics came to be overprescribed to an expanded group of bipolar patients, the concept of a spectrum would not be advancing good clinical practice. The burden of proof should lie on those who are already providing these off-label prescriptions. In particular, we know little about the impact of a rapid increase in the diagnosis of bipolar disorder for children and adolescents86—and along with it, the greatly increased prescriptions of these very agents.87

We should be humbled by recent research on antidepressants, which has shown that these useful drugs do not consistently produce remissions.88 One explanation is that these drugs are being prescribed to a heterogeneous group of patients.1 That is why the acid test for the bipolar spectrum would be to determine whether the symptoms that it attempts to explain either fail to respond, or respond in no more than a partial way, to mood stabilizers.
The concept of a broad bipolar spectrum is a hypothesis that bears investigation but that has not been supported by convincing evidence. And there is evidence that bipolarity is, indeed, being overdiagnosed in practice, with the consequence that patients not meeting research criteria and having no family history of bipolar disorder are identified as falling within the spectrum.

In the history of medicine, physicians have expressly aimed to treat disease on the basis of a detailed understanding of the mechanisms behind pathology. But just as often, physicians develop cures and then go in search of diseases. We should be cautious about rushing ahead to offer panaceas aiming to treat disease on the basis of a detailed understanding of the mechanisms behind pathology. But just as often, physicians develop cures and then go in search of diseases. We should be cautious about rushing ahead to offer panaceas.

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