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Review Article

Validity and utility of bipolar spectrum models

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The bipolar spectrum model suggests that several patient presentations not currently recognized by the DSM warrant consideration as part of a mood disorders continuum. These include hypomania or mania associated with antidepressants; manic symptoms which fall short of the current DSM threshold for hypomania; and depression attended by multiple non-manic markers that are associated with bipolar course. Evidence supporting the inclusion of these groups within the realm of bipolar disorder (BP) is examined. Several diagnostic tools for detecting and characterizing these patient groups are described. Finally, options for altering DSM-IV criteria to allow some of the above patient presentations to be recognized as bipolar are considered. More data on the validity and utility of these alterations would be useful, but limited changes appear warranted now. We describe an additional BP Not Otherwise Specified (BP NOS) example which creates a subthreshold hypomanic analogue to cyclothymia, consistent with existing BP NOS criteria. This change should be accompanied by additional requirements for the assessment and reporting of non-manic bipolar markers.

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Socrates was instructed in 'the art of definition' in the following passage from Plato's *Statesman*:

> *We must beware lest we break off one small fragment and then contrast it with all the important sections that have been left behind.* ***We must only divide where there is real cleavage****… it is splendid if one really can divide off the class sought for immediately from all the rest – that is if the* ***structure of reality*** *authorizes such divisions.* [(1); bold added].

Does the structure of reality of mood disorders allow cleavage of discrete diagnostic categories, or are mood disorders better considered as a continuous spectrum? As reviewed by Kendall and Jablensky (2), diagnostic validity – accurately capturing the 'structure of reality' – ultimately depends on an understanding of the aetiology of an illness. Yet with the exception of some specific entities, such as Huntington's disease, psychiatric diagnoses are not based on an understanding of pathophysiology. In the absence of such understanding, diagnostic standards have relied primarily on overall phenomenology and disease course. The success of the DSM in these and other dimensions of validity (3) has recently been reviewed by Vieta and Phillips (4), with regard to bipolar diagnosis, and found wanting. Yet in the end, the primary justification for a diagnostic system is its utility (5).

The DSM and ICD systems, so-called 'categorical' models, have proven useful, facilitating considerable gains in research since the DSM initiated this system of dichotomous (present/absent) decision making. But intermediate cases suggest that the symptoms and signs constituting bipolar disorder (BP) may be continuously, not dichotomously, distributed; there may be no point of 'real cleavage'. This recognition has led some clinicians and researchers to call for a diagnostic model which formally recognizes a continuous spectrum of bipolar disorders.

Reflecting its use in the current literature, the term 'bipolar spectrum' will refer herein to the

JP serves on the speakers bureau for GlaxoSmithKline, AstraZeneca, and Abbott; does not own any stock in these or other pharmaceutical companies; and has posted an extended discussion of these relationships on his website, PsychEducation.org. He receives royalties from a book for patients and families based on the bipolar spectrum concept. JA serves on the speakers bureau for Eli Lilly & Co., GlaxoSmithKline and AstraZeneca; has received honoraria from Pfizer; owns no stock in these or other pharmaceutical companies; and his work is supported by a private foundation. JK and JS have no conflicts to declare.

putative continuum between unipolar depression and bipolar I (BP I). Other relevant spectra include the possible continuum between infrequent bipolar episodes and continuous cycling, i.e., cycle rate as a dimensional concept. This has been reviewed by Bauer et al. (6) in this issue. Another such spectrum is the possible continuum of mixed states, from those meeting full manic and full depressive criteria, to depression which appears purely unipolar with but a few or even a single manic symptom (7). Third is the apparent spectrum between bipolar disorder and schizophrenia, where the Kraepelinian distinction between the two has been eroded by recent genetic findings (8). Fourth, a spectrum between bipolar disorder and borderline personality disorder has been invoked (7, 9). While this remains highly controversial (10), some data indicate an association greater than seen in other personality disorders (11).

Finally, an aspect of bipolar disorder relevant to the bipolar spectrum is the apparent continuum of symptom presentation from 'normal' to pathologic. Kraepelin (12) himself noted that 'wherever we try to mark out the frontier between mental health and disease, we find a neutral territory, in which the imperceptible change from the realm of normal life to that of obvious derangement takes place'. Vieta and Suppes (13), in this issue, have examined this continuum looking for the appropriate minimal criteria for hypomania [and thus the lower border of bipolar II (BP II) diagnoses]. They observe that while there are many studies which examine differentiation of bipolar II from bipolar I, far fewer data are available to help characterize this lower border of bipolar II.

Given these recent analyses, we have restricted our scope herein to the putative unipolar–bipolar continuum. Reviewing evidence to date, we find evidence for including in the realm of bipolar disorder three groups of patients which are not captured by the current DSM system. After presenting these groups, four diagnostic tools which incorporate a spectrum perspective are discussed. From all this we derive a model for organizing the bipolar spectrum perspective in both categorical and dimensional terms. Advantages and disadvantages of the spectrum perspective on diagnosis are examined briefly, then we present several options for changes in current diagnostic nomenclature. Other recent reviews of the bipolar spectrum present different emphases (14–21).

Three groups of patients on the putative bipolar spectrum

Intermediate forms of bipolarity, lacking full mania, have been recognized for over 100 years. Hecker and Kahlbaum each independently characterized a relatively benign form of manic-depression they called cyclothymia in a series of papers in the 1880s (22, 23). At least since Franz Kallmann's (1938) and Seymour Kety's (1968) appropriation of the 'spectrum disorder' concept for genetic studies of psychopathology, this continuum concept has been used with success in testing psychopathology-relevant phenotypes as heritable traits (24). Some of the more recent diagnostic schema for a bipolar spectrum are shown in Table 1.

Although they differ in numerous respects, these classification systems, taken together, identify three groups of patients as potentially belonging to a bipolar spectrum:

1 Those with hypomanic reactions to antidepressants, e.g., Klerman's BP IV and Akiskal's BP III.
2 'Subthreshold' patients whose hypomania falls shy of current diagnostic cut-offs but who clearly have more than major depressive features alone.
3 Those who lack hypomania by history but have other indications of bipolarity, such as repeated recurrence of depression, family history of bipolar disorder and/or early onset (e.g., bipolar spectrum disorder, Bipolarity Index).

Group 1. Hypomania associated with antidepressants

The DSM-IV (25) explicitly disallows patients whose only manifestation of bipolarity is a hypo-

Table 1. Diagnostic schema for a bipolar spectrum

Authors	Year	System	Criteria
Akiskal et al. (29)	1977	Cyclothymia-bipolar continuum	'Intuitive' selection then prospective evaluation
Angst (88)	1978	Bipolar subtypes along a spectrum	Retrospective subgrouping
Klerman (30)	1981	Categories I–VI	Literature review of the 'spectrum of mania'
Akiskal and Pinto (31)	1999	Categories I–IV including 1½, 2½, 3½	Narrative, case illustrations
Ghaemi et al. (50)	2002	New category: 'bipolar spectrum disorder'	List of non-manic bipolar markers; DSM-like schema
Angst et al. (46)	2003	Add minor bipolar disorders	Epidemiology based
Sachs (67)	2004	100-point 'Bipolarity Index'	Bipolar markers grouped in five dimensions

mania or manic reaction to an antidepressant medication. Yet in two long-term follow-up studies, 100% of such patients ultimately manifested overt bipolarity (26, 27). One of these studies followed a cohort of 60 adolescents who had been hospitalized for major depression, with no prior history of mania (26). Remarkably, all 60 patients were followed for 3–4 years. During that time, 100% of those who manifested hypomania on an antidepressant (within two weeks of initiation) acquired a diagnosis of bipolar disorder by Research Diagnostic Criteria – yet there were only two such patients.

By contrast, in an earlier study in young adults, Akiskal et al. (27) followed 206 patients who had presented to an outpatient clinic with depression. During an average follow-up period of three years (range: 1–9 years), 20% of the group developed mania. Of the initial 206 patients, 18 patients (32%) had before presentation experienced an antidepressant-associated hypomania (within four weeks of antidepressant initiation). All of these patients had a manic episode during follow-up. None of the patients lacking antidepressant-associated hypomania had a bipolar course. Thus while the sensitivity of antidepressant-associated mania, as a bipolar marker, was 32%, the specificity was 100% – i.e., every patient who presented in unipolar depression with that sign went on to a bipolar course. Such a presentation is common: in a recent study of university students with depression, 16% had a history of an antidepressant-associated hypomania (28).

Group 2: Subthreshold hypomania

History. In 1977 Akiskal et al. (29) characterized 'subaffective disorders' that merge imperceptibly with the bipolar II (and sometimes bipolar I) forms of manic depressive illness. This theme of subthreshold bipolarity continues through more recent classification schema. Klerman (see 30, p. 14), for example, posited an intermediate state between normal happiness and hypomania, which he termed 'neurotic elation'. In general, the trend over the period of time shown in Table 1 has been toward a greater willingness to consider lower set-points for the minimum criteria for hypomania. The problem with lowering cut-offs, as Akiskal and Pinto (31) point out in their 1999 review and subtype proposal, is that setting the bar for a diagnosis anywhere below full mania makes the condition difficult to define operationally. However, of note here are studies of inter-rater reliability for hypomania and bipolar II which show that expert clinicians have very high reliability scores (32, 33). Nevertheless, in theory at least, when lowering the bar yet further, below current criteria for hypomania, the problems of threshold detection and thus inter-rater reliability inevitably become greater. Two means of coping with this inherent problem of diminishing specificity and reliability include a probabilistic approach and a dimensional approach, discussed further below.

Phenomenology. Referring originally to bacterial classification, Sneath (34) described 'points of rarity', akin to Plato's 'natural points of cleavage', which might serve to distinguish one group of organisms from another. Following on this concept, Kendell and Jablensky's review (2) decries the lack of studies specifically examining the presence or absence of 'zones of rarity' between unipolar and bipolar disorder. Taking up that challenge, Benazzi (35) looked specifically for such gaps along the continuum of symptoms found in patients with major depression and bipolar II [diagnosed with the Structured Clinical Interview for DSM-IV, as modified by Benazzi and Akiskal (36)]. One would expect that a histogram plotting the total number of hypomanic symptoms occurring during depression (effectively, studying degree of mixed state) for all patients in the study would be bimodal: most of the patients with unipolar depression would have few or none, creating one peak on the left of such a graph; and most of the patients with bipolar II would have many, creating a second peak on the right. In this study, however, the histogram curve closely approaches a normal distribution, although slightly skewed toward a low number of hypomanic symptoms (mode = 2). Thus, there were no 'zones of rarity' as would be predicted if the two diagnoses are easily 'cleavable', i.e., consistent with a categorical model. These results derive from the same database Benazzi (e.g., 37, 38) has used to describe the importance of minimal manic symptoms within otherwise 'major depressive episode' presentations. Although Benazzi has strived to maintain rigour in data gathering using a structured interview, there is a risk that his database may subtly mirror his own prior assumptions about the nature of bipolar disorder (i.e., that the DSM categories are too narrow) and that the results above are therefore somewhat tautological. However, this concern is mitigated by Benazzi's replication of this search for zones of rarity using a patient self-rating form, with the same results (39).

In another analysis which also contrasted the symptoms of patients with major depression with those of patients with bipolar disorder, Cassano et al. (40) compared symptoms characteristic of mania in patients with remitted unipolar depression versus remitted bipolar I (clinical diagnoses,

confirmed by the Mini International Neuropsychiatric Interview). These investigators also found no 'zone of rarity' in the sense that manic symptoms were not confined to those with a bipolar diagnosis. These manic symptoms were not detected using DSM criteria, but rather a broad array of 60 items judged to mark bipolarity by these investigators, for which some validation data has been presented [Structured Clinical Interview for Mood Spectrum (41)]. This paper has been criticized for the following logic: symptoms found in patients with bipolar disorder indicate bipolarity; therefore, when those symptoms are present in other patients, those patients have bipolar disorder (42). However, as gently argued in reply by Cassano (43), the report shows that many patients with remitted unipolar depression have in their history symptoms usually associated with the manic side of bipolar disorder; but the primary point is to see that these symptoms lie on a smooth gradient that is not discontinuous with that of patients with bipolar disorder. In other words, there is no 'zone of rarity' in the apparent continuum of manic symptoms (from few, to many) viewed over patients' histories as a whole, and thus no apparent point of 'real cleavage', in Plato's terms.

Epidemiology. Epidemiologic data relevant to the bipolar spectrum concept have been previously reviewed (44, 45). More recently, two large epidemiologic studies have included patients with subthreshold hypomania alongside patients meeting DSM criteria. Angst et al. (46) found a gradient of hypomania in their Zurich cohort – although with only two intermediate points between DSM-IV bipolar II and asymptomatic controls. As shown in Table 2, DSM-IV bipolar II criteria identified a group of patients with the most bipolar features, in this cohort. 'Zurich criteria', both strict and broad, require fewer hypomania criteria than the DSM: for the strict criteria set, the DSM-IV criteria apply except for the duration of episode, where any is allowed; for the broad criteria set, both the duration requirement and the DSM requirement for a change in function are omitted, but other criteria still apply.

Table 2. The gradient of bipolarity across subgroups of BP II disorders

	DSM-IV BP II (n = 12), %	Zurich BP II, strict (n = 33), %	Zurich BP II, broad (n = 44), %	DSM-IIIR MDD (n = 96), %	MDD versus BP II broad (p)[a]
Time with depressive symptoms[b]	75.1	66.4	68.4	65.9	0.716
Time with hypomanic symptoms[b]	68.7	37.9	31.9	7.4	0.000
Endorse 'ups and downs'	50.0	48.5	27.3	19.8	0.319

[a]one-sided test: BP II > MDD.
[b]Percent time symptomatic across 22 years.
BP II = bipolar II disorder; MDD = major depressive disorder.

Because depression is common to both major depressive disorder and all versions of bipolar disorder, the result in the first line of Table 2 is not surprising: there is no difference across this putative spectrum. By comparison, percent time spent with hypomanic symptoms declines from formal bipolar II to major depression. Likewise, the percentage of interviewees endorsing 'ups and downs' of mood shows a declining trend across these groups.

In the most recent iteration of the United States' National Comorbidity Survey, Kessler et al. (47) reported on a subgroup of patients whose bipolar symptoms did not meet DSM thresholds, yet whose disability from these symptoms equalled that of patients with asthma and diabetes. In their work-in-progress, early indications suggest the subthreshold group is the most common form of bipolar disorder, with a prevalence slightly greater than either BP I or BP II (the latter each approximately 1%; Kessler, personal communication to JA, 2006). These findings replicate and extend a re-analysis of the earlier US Epidemiological Catchment Area study (48) which also found that people who had some hypomanic symptoms, but did not meet diagnostic criteria for bipolar II, had levels of disability similar to those meriting a formal diagnosis.

These studies are consistent with the bipolar spectrum model, i.e., that there is a continuum of bipolarity which extends beyond the current minimum threshold for DSM-IV hypomania (and thus beyond bipolar II), toward unipolar disorder; and that there are substantial numbers of people with depression *plus* such subthreshold symptoms. Nevertheless, demonstrating an additional point or two on a presumed line does not establish a continuum. It could be argued that these epidemiologic studies have assumed that 'hypomanic-like' symptoms represent the same phenomenon as a full hypomania or mania meeting DSM criteria, and that this assumption does not allow the possibility that these different clinical presentations may reflect different aetiologies. However, in both the Swiss and American studies, the symptoms studied are DSM-IV manic symptoms, i.e., each *symptom*

meets existing criteria for the disease state, although some patients did not, by virtue of having too few of these symptoms.

Group 3: Bipolarity independent of hypomania or mania

Although a radical departure from the DSM diagnostic approach, the idea of bipolar disorders without overt hypomania or mania is not new. Kraepelin (12) emphasized not mania but rather a high degree of recurrence as the principal identifying feature of manic-depressive course. Klerman (30) included in his 'spectrum of mania' a bipolar V category in which individuals had only depression, no hypomania or mania, but a high familial incidence of bipolar disorder. Since that time, evidence has accumulated for numerous markers of bipolar disorder other than mania or hypomania, sometimes dubbed 'soft signs' (if several are present, with or without subthreshold hypomanic symptoms, this condition has been loosely referred to as 'soft bipolarity').

In addition to recurrence and family history, several other features have been consistently associated with a bipolar course. Hereafter referred to as non-manic bipolar markers [other literature has used the term 'external validating features' (49)] these features can be divided into five realms (50):

(A) Antidepressant-induced hypomania or mania
(B) Course variables: early age of onset (before age 20), postpartum onset, highly recurrent (>5 episodes), presence of rapid cycling, brief episodes (<3 months)
(C) Symptom phenomenology: atypical features (increased sleep or appetite), psychomotor changes, psychotic features
(D) Family history of bipolar disorder in a first-degree relative
(E) Occurrence of the depressive mixed state (a major depressive episode with two or more manic symptoms, excluding psychomotor agitation)

(A) Antidepressant-associated hypomania and mania. Evidence associating this finding and subsequent bipolar course has been examined in the discussion of Group 1 above.

(B, C) Course and phenomenology. Evidence associating these variables with subsequent bipolar course has been reviewed in this issue by Mitchell et al. (51), and elsewhere (52). The Mitchell et al. analysis examines illness course and symptomatology for a total of 52 such variables. They note that in many of the older studies, potentially critical confounds such as medications or demographic factors such as age or gender were often not controlled, nor was there correction for multiple testing. They therefore focused attention on more recent studies in which these variables were addressed. They conclude that among the illness *course* variables, two are sufficiently strongly associated with bipolar outcomes to be useful in distinguishing bipolar from unipolar depression: early age of first depressive episode; and a large number of depressive episodes. They find that more research is necessary to determine cut-points for early onset, as previous studies have sometimes used age 20, sometimes age 25. Similarly, the particular number of prior depressive episodes which best discriminates unipolar from bipolar depression has also yet to be determined.

Among the *phenomenology* variables (symptoms and mental status examination signs) examined by Mitchell et al. (51), they emphasize four that distinguish bipolar from unipolar depression: atypical features (increased sleep or appetite); psychomotor changes; psychotic features (and pathological guilt) and lability of mood. The latter does not appear on many lists of 'soft signs'; it derives from a prospective study of 'switching' from unipolar to bipolar course (52).

These variables, by themselves, clearly do not define the presence of bipolar disorder. Although consistent differences in group means have been observed, none of them has sufficient specificity to discriminate, by itself, bipolar from unipolar disorder (with the possible exception of antidepressant-associated hypomania or mania). For example, in one study (27) the mean age of onset in bipolar disorder was 26.1 (the modal value was substantially lower), versus a mean age of onset in unipolar depression of 35.5 – but the standard deviations were 13.3 and 15.3, respectively. On this basis Mitchell et al. (51) conclude that there appears to be no gap (no 'zone of rarity', as above) between unipolar and bipolar disorders.

(D) Family history. One non-manic marker of bipolarity, family history of bipolar disorder, deserves special consideration, as it may represent what little we know about genetics from a spectrum point of view. A major source for the bipolar–unipolar distinction, originally devised by Leonhard (53), was genetic data from the 1960s which seemed to indicate differential familial transmission in these two proposed subtypes of affective disorders (54). These genetic data were influential in the change in 1980 with DSM-III

whereby the broad manic-depressive illness concept derived from Kraepelin was divided into the bipolar/unipolar subtypes. Hence family history is central to the whole dichotomy, and thus the presence of a bipolar family history in an individual seen as having unipolar depression would potentially be an anomaly. Recent genetic research indicates more overlap in bipolar and unipolar familial transmission than appeared to be the case in earlier studies (55). However, looking at genes in separate individuals with same diagnosis (e.g., bipolar I) is inherently flawed as it presumes that they both have the same biologic illness despite non-identical phenotypic expressions. Thus, the heterogeneous nature of the affective phenomenologies may be reflective of multiple genes at work (56), a discordant network of genetic transmissions *per se*, which suggests again that even at the genetic level there is no 'zone of rarity.' Of course, none of these possibilities is definitive and further research is required to clarify the nosologic import of the genetic transmission of bipolar disorder.

(E) Mixed states. Subthreshold hypomanic symptoms occurring *simultaneously* with symptoms of major depression present another diagnostic conundrum. These cannot be regarded as a mixed state using current DSM-IV criteria, which admit only of full mania accompanying full major depression. Indeed, patients with such symptoms cannot be regarded as 'bipolar' at all. Yet, these patients are more similar to patients with bipolar disorder than unipolar disorder with regard to non-manic bipolar markers such as age of onset and family history (57, 58). However, no consensus exists on how to handle these patients diagnostically: even patients who have substantial but subthreshold manic symptoms (e.g., racing thoughts, pressured speech and increased motor activity) were considered controversial regarding their categorization (59). Nevertheless, for depressed patients with subthreshold manic symptoms who have never experienced a hypomanic or manic episode, consideration of bipolarity may be critical when considering treatment approaches (60). A spectrum perspective has been invoked as one means of coping with this boundary problem (57).

Not included in this list of non-manic bipolar markers is the concept of 'instability'. As summarized by Swann et al. (61), whereas current criteria emphasize manic and depressive episodes, bipolar disorder is an illness that confers abnormal *susceptibility* to these states. In the long run, greater focus on mood instability as a potential core feature of bipolar disorder is likely warranted.

Non-manic markers: conclusion

Although 'soft signs' and 'soft bipolarity' may not be ideal terms, they do capture the inability of non-manic markers to separate bipolar from unipolar, independent of a history of hypomania or mania. Such markers only signal an increased likelihood of a bipolar outcome. It can be asked why a condition with no mania or hypomania should be given a label of 'bipolar disorder' at all. Highly recurrent depression, for example: although this is statistically associated with a bipolar outcome, why call it 'bipolar' until hypomania or mania develops? This question does indeed seem puzzling unless one considers the implications of the presence of *several* non-manic markers appearing together (considered alone, none warrants invoking the bipolar label, with the possible exception of antidepressant-associated hypomania or mania). Antidepressants are useful and relatively safe for unipolar depression, but carry several recognized (and several controversial) risks in bipolar patients. Thus antidepressants are relegated to augmentation roles in nearly all bipolar treatment guidelines. How many non-manic markers can a patient have before her/his depression need be regarded as sufficiently 'bipolar' to warrant avoiding the use of antidepressants as initial monotherapy? This is not idle speculation: Frye et al. (62) recently reported that in bipolar depressed patients, a Young Mania Rating Scale score of as little as 4 predicted twice the antidepressant switch rate compared with the complete absence of manic symptoms; but this concern cannot be resolved using existing data.

In the above analysis, subthreshold hypomania and non-manic bipolar markers were considered separately. However, much more likely is a co-occurrence of the two. Indeed, many variations are possible, combining the multiple non-manic markers and the numerous ways in which manic symptoms can fall short of DSM criteria for hypomania (number, intensity or duration of symptoms). At present, none of these variations can be regarded as bipolar, even when many non-manic markers are present and criteria for hypomania are nearly met. This is the nature of a categorical system: a cut-off must be placed somewhere, even though many patients may lie just below that threshold.

Spectrum-based diagnostic tools

Several diagnostic instruments have been put forth which incorporate a bipolar spectrum perspective

in some way and therefore might capture subthreshold patients. Here are four such instruments, which illustrate a range of options for changes in the current diagnostic system, from minimal to substantial.

The Bipolar Spectrum Diagnostic Scale

This patient self-report scale is a categorical instrument, in that it is designed to judge whether a bipolar disorder is present or absent. It was originally developed by Ron Pies and subsequently studied by Ghaemi et al. (63). A descriptive paragraph presents multiple aspects of mood course in bipolar disorder, and patients are asked to endorse any of 19 aspects of mania and depression. In this respect it differs only slightly from another commonly used patient self-report system, the Mood Disorders Questionnaire (MDQ) (64), which by a yes-or-no format queries 13 symptoms of mania. However, the Bipolar Spectrum Diagnostic Scale (BSDS) was designed to be used with a *probabilistic* scoring system, in which the patient is offered a likelihood of bipolar disorder rather than an absolute, yes-or-no answer (this version is available on the internet; see 65). With a maximum score of 25, a 19 or greater indicates 'bipolar spectrum disorder highly likely'; 11–18, 'moderate probability of bipolar spectrum disorder'; 6–10, 'low probability of bipolar spectrum disorder' and <6, 'bipolar spectrum disorder highly unlikely'.

To test the sensitivity and specificity of this instrument, however, a cut-off scoring system is required to allow comparison in a standard 2×2 table versus a gold standard, in this case a comparison with clinicians' DSM-IV diagnosis (63). Therefore an analysis of discriminant validity using the probabilistic system has not been conducted. Some evidence suggests that using a cut-off scoring system, the BSDS has greater sensitivity for bipolar II than the MDQ (63), with adequate accuracy (66).

Probabilistic reasoning

Another probabilistic system is presented in this issue by Mitchell et al. (51). After their review of non-manic bipolar markers, described above, they propose that if a patient's depression includes a certain number of such markers (the optimal number to be determined through further research), then a greater likelihood of bipolar disorder should be considered. They are not proposing a system to detect *degrees* of bipolarity. By proposing a cut-off value, they explicitly remain within a categorical perspective. The point of assessing non-manic bipolar markers is to increase or decrease the *probability* that bipolar disorder is the basis for the patient's depression. The value of this system lies in their well-researched list of non-manic bipolar markers; and also in their having formalized (as Pies did with the BSDS) the possibility of diagnosing bipolar disorder as a matter of *probability* rather than as an absolute yes-or-no issue.

The Bipolarity Index

By contrast, the only system proposed to date which allows for the illness to exist as a matter of *degree*, and places patients on a presumed continuum of bipolarity, rather than diagnosing them as bipolar *or* unipolar, is the Bipolarity Index. This instrument is currently in use as part of the Massachusetts General Hospital (MGH) Bipolar Clinic's Affective Disorders Evaluation. It has not been validated, or normed relative to controls or bipolar patients. It has not been published, only alluded to in a review article (67). One of the progenitors, Gary Sachs, has described in an interview the manner of its use at MGH, including an emphasis on its investigational status (68). The utility of the Bipolarity Index, at this untested stage, is that it presents a model for organizing non-manic bipolar markers, and encourages and systematizes that information gathering, with quantitative anchor points.

In the Index, bipolar markers are organized in five dimensions, each worth 20 points, for a 100-point total scale:

1 Episode characteristics
2 Age of onset
3 Course of illness/associated features
4 Response to treatment
5 Family history

Episode characteristics include hypomania or mania (DSM criteria *and* subthreshold versions); and depression, including atypical features, postpartum onset and psychosis. Age of onset simply asks for the age at which the first affective episode took place. Course of illness includes degree of recurrence but also an assortment of less well-demonstrated bipolar markers such as perimenstrual exacerbation and some features of hyperthymia [by contrast, brevity of episodes has more data in support of its inclusion on such a list (50)]. Response to treatment includes either a positive response to mood stabilizers or an adverse reaction to antidepressants. Family history ranges from a bipolar first-degree relative; through unipolar depression; substance use; and more distant

relations; to any relative with a diagnosis-related condition (anxiety disorders, eating disorders, attention-deficient disorder/attention-deficient hyperactivity disorder).

There are no published data on the optimal weightings each of these features should be given, which at present range from two points (e.g., for more than two advanced education degrees) to 20 (e.g., full recovery within four weeks on a mood stabilizer). For now, each dimension is weighted equally. Nor have any data been reported yet on the meaning of a given value on this 100-point scale, although Sachs has commented that around 60 points appears to be the range where a patient with classic lithium-responsive manic-depression might fall (67). He has advocated using the Bipolarity Index for a spectrum-based view *alongside* the DSM categorical system, emphasizing that the Index approach helps structure data gathering (68).

Bipolar spectrum disorder

Categorical criteria characterizing a version of bipolar disorder lacking hypomania or mania were proposed by Ghaemi et al. (50). They called this bipolar spectrum disorder. After reviewing the literature on the non-manic bipolar markers described above, they presented a system using these markers in a DSM-like approach of criteria and cut-offs. The system is designed to apply to patients who have had at least one episode of major depression, but no episodes of hypomania or mania by DSM criteria. Their organization and weighting of non-manic bipolar markers is shown in Table 3.

Table 3. Bipolar spectrum disorder criteria

A. At least one episode of major depression
B. No history of spontaneous hypomania or mania
C. Either of the following, plus at least two items from criterion D, or both of the following plus one item from criterion D:
   1. A family history of bipolar disorder in a first-degree relative
   2. Antidepressant-induced hypomania or mania
D. If no items from criterion C are present, six of the following nine criteria are required:
   1. Hyperthymic personality (at baseline, non-depressed state)
   2. Recurrent major depression (>3 episodes)
   3. Episodes of major depression are brief (<3 months, on average)
   4. Atypical depression symptoms by DSM criteria
   5. Psychosis during depression
   6. Early age of onset of major depression (<25)
   7. Post-partum depression
   8. Antidepressant loss of response (acute but not prophylactic response)
   9. Lack of response to >3 antidepressant trials

Although in their review they present a diagram showing this 'bipolar spectrum disorder' as a continuum extending between bipolar II and highly recurrent unipolar depression, with the criteria in Table 3 they create a categorical entity, i.e., a condition which is either present or absent. In a later report they described this manoeuvre as a compromise between a strictly dimensional and a strictly categorical system (69).

Views of the bipolar spectrum

Note that all these tools in some way assume a continuum from unipolar to bipolar disorder. Several introduce the concept of probabilistic reasoning to replace or augment the absolute criteria of the DSM: either by admitting that detecting bipolar disorder may be less than certain, and better characterized as a range of probabilities; or by admitting that bipolar disorder itself may be present *in degrees*. Some incorporate non-manic markers shown by longitudinal follow-up to be associated with a greater likelihood of bipolar outcome. These various approaches are illustrated in Figure 1, which compares categorical and dimensional ways of thinking about the presumed bipolar spectrum.

The categorical view (Fig. 1A) characterizes particular variations as *nodes along a continuum*. This is analogous to the visual spectrum, in which the terms 'red' and 'green' refer to points on a continuous electromagnetic spectrum. In this view, a revised DSM system could incorporate a spectrum perspective without abandoning its categorical approach, by adding additional nodes such as bipolar III. Also shown is bipolar spectrum disorder, discussed above, appearing here nearest to unipolar depression, reflecting the absence of manic symptoms but the presence of non-manic bipolar markers.

In the dimensional view (Fig. 1B), each of the variables associated with bipolar outcome is shown as a continuum along which the degree of bipolarity increases. One could also view this continuum as depicting the *probability* of bipolar disorder: this is akin to asking the question 'Do you have bipolar disorder?' and presenting the answer as a *likelihood*. But in the usual sense of a dimensional view, the continuum shown in Fig. 1B is akin to asking 'How bipolar are you?' and presenting the answer as a matter of degree, as advocated by Sachs in his discussion of the Bipolarity Index (68). Whether bipolar disorder is best considered a disease which is either present or absent, and thus for which these variables give information on the likelihood of its presence; or whether instead bipolarity is a

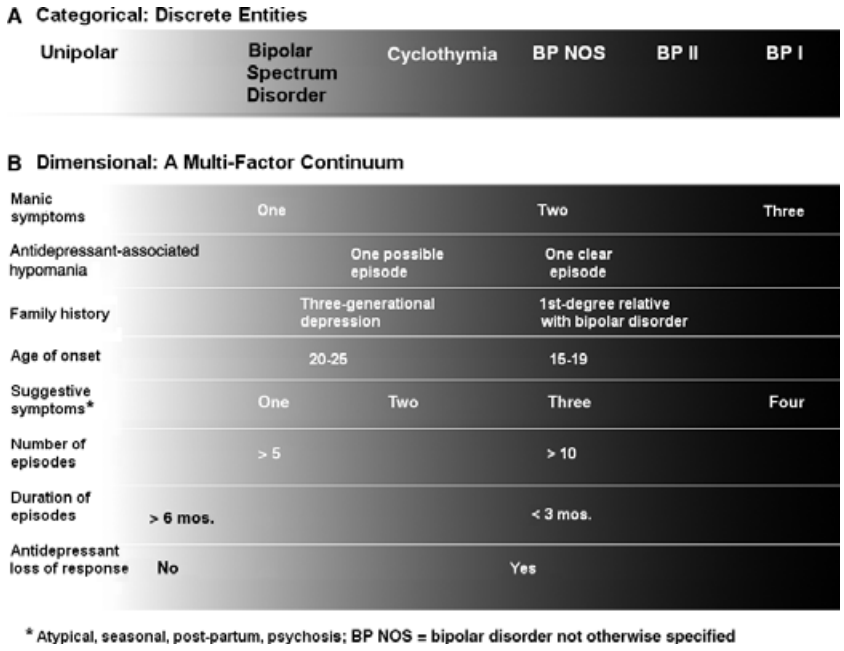

Fig. 1. Two views of the bipolar spectrum.

phenomenon with no 'points of real cleavage' at which to divide it, in Plato's terms, from major depression (i.e., a true unbroken continuum from unipolar to bipolar presentations), remains to be determined on the basis of its aetiology. For example, if a gene involved can have varying degrees of penetrance, a continuum of symptoms could result. Alternatively, a gene might be identified which is either expressed fully, or not at all, creating a potential cleavage in presentations: in this case, the hypothetical gene effect, if detectable, would either be present, or not.

Unfortunately, with the exception of the first variable [the number of hypomanic symptoms; see the review in this issue by Vieta and Suppes (13)], none of these indicators has been studied sufficiently to allow quantification of bipolarity (degree or likelihood) on the basis of their presence, or absence, or extent. Thus the positioning of the indicators shown in Fig. 1B is for demonstration only, illustrating that each of these variables may be a continuum itself, and that each can contribute to a varying degree of bipolarity for a given patient. For example, is a first episode of depression at age 15 clearly a stronger indicator for bipolarity than a first episode at age 21? Are depressive episodes lasting 3 months really more likely to be 'bipolar' than episodes lasting, say, 4 or 5 months? These questions have yet to be answered; nor the parallel questions for each of the variables shown. This lack of data makes establishing cut-off points for these variables potentially arbitrary at present.

Some might regard making spectrum-oriented changes to current diagnostic criteria as premature, given this lack of data. It is even uncertain, at this point, whether non-manic markers and subthreshold manifestations of bipolarity reflect the same biologic mechanisms as classical bipolar disease. On the other hand, the bipolar spectrum concept is now widespread in the literature (e.g., 14–21), as also shown herein by four diagnostic tools dedicated to this perspective. Therefore a comparison of the potential risks and benefits of altering the current diagnostic system is warranted. Some of the most important are considered below.

Advantages and disadvantages of incorporating a spectrum perspective

Diagnostic accuracy

Some psychiatrists believe that the pendulum of diagnosis has already swung too far towards overdiagnosis of bipolar disorder (70–74), although there is considerable empirical evidence to the contrary (75). Yet the terms 'over- and underdiagnosis' refer to some sort of standard for determining what the patient 'really' has, which is the very issue under debate. To escape this circular reasoning, reliance on other indicators of diagnostic accuracy is necessary. As concluded by Mitchell

et al. (51) in this issue, in the absence of biological markers, predictive validity is one of the most important features of a diagnosis, particularly for clinicians: prediction of efficacy of treatment, and of adverse response; and prediction of long-term course. The data presented above suggest that non-manic features such as age of onset, family history and so forth are predictive of bipolar outcomes, although not sufficient unto themselves for this purpose. Clearly, they should be regularly assessed by clinicians; the question is how these markers should be incorporated into the diagnostic process.

Logistics

Too many overhauls of psychiatric nosology in less than a century could add to diagnostic chaos rather than diminish it. Most clinicians currently practicing were trained using a categorical model. Shifting from a categorical to a fully dimensional system would require a massive retraining effort for mental health professionals akin to that required when DSM-III was introduced in 1980 (5). In addition, many administrative systems (e.g., insurers, government programmes) are based on our current categorical system. These too would require a tremendous reorganization to accommodate a complete shift to a dimensional model. A minor change incorporating some aspects of a spectrum perspective into the existing categorical system would have tremendous advantages relative to a major shift in diagnostic approach. The latter could only be justified on the basis of substantial evidence and clinical necessity.

Impact on clinical practice

Few data exist on which to base conclusions here. At minimum a more inclusive view of bipolarity would likely invite broader use of mood stabilizers (using the term broadly), which is of concern given their risks such as weight gain, hyperglycemia and other adverse metabolic shifts; skin reactions from acne to Stevens-Johnson Syndrome; tardive dyskinesia; and others, as well as substantial side effect burden for many agents. It could be argued that this broader use is already underway, but perhaps not to the full extent likely to follow a diagnostic shift. On the other hand, a more inclusive view of bipolarity would also suggest that concerns about adverse effects of antidepressants in bipolar patients (75–78) might apply to patients not currently regarded as at risk for such reactions: e.g., switching into mania, cycle acceleration, induction of mixed states and perhaps even induction of suicidality. Although in the view of many the data may not support the action, regulatory agencies of the USA and UK have already forced this issue all the way to the other end of the bipolar spectrum by invoking potential increases in suicidality in *unipolar* patients receiving antidepressants.

There are many other considerations as well, such as maintaining the integrity of the bipolar diagnosis for research purposes (79), the risk that current interest in the spectrum perspective represents a transient phenomenon (5, 70), and whether a spectrum perspective would increase the risk of stigmatizing patients with a bipolar label versus making it easier for them to accept *degrees* of bipolarity. None of these considerations leads to a clear course of action. Several options are presented below.

Recommended changes in the DSM-IV

A note of caution: important concerns have been raised about pharmaceutical companies influencing the development of guidelines from which those companies would directly benefit (80–82). These concerns clearly apply to the following recommendations as well. Although there are alternative ways to view corporate involvement in such clinical affairs (83, 84), we should note that two of the authors of this paper (JA, JP) have received numerous and substantial honoraria from pharmaceutical companies which could benefit from a broadening of diagnostic criteria. However, both have repeatedly presented the same ideas discussed herein *prior* to the receipt of such funding (see 46, 85 respectively). Grants from Organon and Solvay funded activities of the International Society for Bipolar Disorders' (ISBD) Committee on Diagnosis, including partial funding of a staff member's salary and the publication costs of this supplement. Committee members met twice during ISBD annual meetings for which they funded their own transportation and other expenses. No other industry influence was sought or allowed.

On the basis of the data reviewed herein, we believe that several changes in current diagnostic system warrant consideration: (Option 1) formal recognition of non-manic bipolar markers, either by adding an additional category such as bipolar III, or modifying the BP NOS criteria, or by using a dimensional system alongside the current categorical system; and (Option 2) recognizing bipolarity without hypomania or mania, either by formalizing bipolar spectrum disorder or via further modification of BP NOS criteria. These options are examined briefly below.

Option 1: Formal recognition of non-manic bipolar markers

(A) Bipolar III. Non-manic bipolar markers could be used to delineate a new category, 'bipolar III', defined as subthreshold hypomania with full major depression accompanied by additional indicators of bipolar disorder. Note that this parallels an existing category, cyclothymia, which allows for subthreshold depressive symptoms in the presence of full hypomania. In bipolar III, thus defined, the subthreshold 'pole' is simply reversed. Adding bipolar III has the advantage of logically continuing the description of bipolar variations – from bipolar I, to bipolar II, and thence to bipolar III – in accord with clinical and research observations. It has the disadvantage of potential confusion, because the term is widely used in formal and lay (e.g., internet) literature to refer to antidepressant-induced hypomania. There could also be some disadvantage in expanding the number of bipolar categories, as proliferation thereof has already been criticized for making it difficult to recognize and successfully discriminate between them (86). In our view, this makes the following option preferable.

(B) Modify BP NOS. Alternatively, non-manic markers could be incorporated into the DSM by adding another example in the BP NOS criteria, appearing in 'italics' below the current BP NOS criteria in Table 4.

Note that in the current DSM BP NOS category, Example no. 1 describes symptoms which do not meet *duration* criteria (see Table 4). The proposed modification adds an example describing cases which do not meet criteria for *number or intensity* of manic symptoms. However, to maintain and perhaps improve diagnostic rigour, this inclusion is accompanied by a requirement for documentation of non-manic markers. How many, or which non-manic markers should be present to support a BP NOS diagnosis on the basis of subthreshold hypomanic symptoms? This could be specified categorically, i.e., with a cut-off minimum. However, current data do not describe an optimal cut-off point, with the clear exception of antidepressant-induced hypomania/mania, which appears to mark bipolar outcomes quite specifically. A dimensional view would suggest that in this particular instance, cut-offs could be replaced by rigorous description of non-manic markers, as per Table 4. If clinicians or researchers needed to use a cut-off, precedents have been set in the bipolar spectrum disorder criteria (Table 3).

(C) Use a dimensional system alongside the DSM. This approach has been advocated by one of the authors of the Bipolarity Index, which is the primary example of such a system (68). This five-dimensional system requires systematic gathering of information about non-manic bipolar markers. But it differs from the DSM modifications above by allowing characterization of *degree* of bipolarity. This represents a significant departure from the DSM system, perhaps accounting for the lack of fanfare with which the Index has been introduced. Such reticence is warranted at this point in that no data have yet been presented demonstrating either validity or utility of this approach. Nevertheless, it is a simple system for organizing the non-manic bipolar markers alongside assessment of manic symptoms, worthy of significant attention on that basis alone. We agree with one of the authors of the Bipolarity Index, who emphasized that it could be used alongside the DSM-IV as an additional diagnostic perspective (68).

Table 4. Bipolar disorder not otherwise specified (BP NOS) criteria with a spectrum-based addition

296.80 Bipolar disorder not otherwise specified
The BP NOS category includes disorders with bipolar features that do not meet criteria for any specific bipolar disorder. Examples include: 1. Very rapid alternation (over days) between manic symptoms and depressive symptoms that do not meet minimal duration criteria for a manic episode or a major depressive episode. 2. Recurrent hypomanic episodes without inter-current depressive symptoms. 3. A manic or mixed episode superimposed on a delusional disorder, residual schizophrenia or psychotic disorder not otherwise specified. 4. Situations in which the clinician has concluded that a bipolar disorder is present but it unable to determine whether it is primary, because of a general medical condition, or substance induced. 5. *Manic symptoms that do not meet minimal criteria (by number or intensity) in the context of multiple other signs of bipolarity*.* **Clinicians should specify precisely which such signs are present and include this list in their assessment statement, as follows:* *a. Family history (bipolar diagnoses, multi-generational mental illness, alcohol and other substance use, suicides)* *b. Depressive symptom phenomenology (atypical, seasonal, psychomotor disturbance, psychosis)* *c. Course of illness (early age of onset, post-partum onset, short duration of episodes and greater number of episodes)*

Option 2: Bipolar disorder without hypomania or mania

As described above, this idea is not as radical as it sounds, given its history, despite how much it

departs from the DSM criteria for bipolar disorder. Table 3 herein presents a categorical system for recognizing this variation, as proposed by Ghaemi et al. (50). As shown in Fig. 1A, their bipolar spectrum disorder could represent another 'node' on a bipolar continuum. Another option would be to add one more example to the BP NOS criteria, as shown above for subthreshold hypomania, as follows:

*6. Multiple signs of bipolarity without hypomanic or manic episodes (also known as bipolar spectrum disorder)**

The asterisk refers to the same addendum in Table 4 in which clinicians are instructed to specify precisely which non-manic bipolar markers were detected, from the dimensions of family history, symptom characteristics, and course of illness. Adding this example would formalize recognition that variations of bipolar disorder which lack the current cardinal indicator of hypomania or mania are possible, while preserving a system of categories rather than a fully dimensional system such as the Bipolarity Index. However, in the preparation of this paper significant 'dissensus' was identified regarding whether the existing literature supports incorporation of this group of patients as 'bipolar'. Accordingly, further research is warranted in this area.

Discussion

A recent study of borderline personality disorder diagnosis by Westen et al. (87) demonstrates the validity and utility of an approach based on 'prototypes': single-paragraph descriptions of characteristic patient presentation. This study serves as an example of the kind of analysis warranted for any new diagnostic approach: the authors demonstrate the validity of their approach by presenting data which show that a prototype-derived diagnosis correlates strongly with measures of patients' adaptive functioning and response to treatment; and demonstrate utility by presenting data on clinician satisfaction with this approach, relative to the current system. To date no such research has been presented for any spectrum-based diagnostic system. On that basis it could be argued that making any change now is premature.

On the other hand, the data reviewed herein are consistent with a view of bipolar disorder as a continuum of illness lacking any point of 'real cleavage', in Plato's terms, from unipolar depression. These data also strongly suggest that the non-manic bipolar features reviewed above are associated with bipolar outcomes. These features can be used to adjust the prior probability of bipolarity before a final determination is made on the basis of the presence or absence of manic symptoms, whether that is captured by use of a screening tool like the MDQ or by clinician interview. Therefore even now, at minimum, incorporating the assessment of non-manic bipolar features into the diagnostic process is warranted. The question is how to do this.

The Bipolarity Index provides a convenient means of organizing this information along with any history of hypomania or mania. It can be used to convey this information in patient charts, so that discussions about whether bipolar disorder belongs in the differential can be based on this entire dataset. In the future, we may learn how to apply particular weights to variables in the Index and how to interpret the total score. However, it cannot easily integrate with the DSM system. As one of its authors has suggested, at minimum it can be used alongside the DSM-IV as an additional heuristic.

However, to target broader change in clinician understanding and behaviour, an interim change in the DSM-IV would likely have greater impact than advocating simultaneous use of the Bipolarity Index. Existing BP NOS examples already include patients who fall below the bipolar II threshold because their symptoms do not meet *duration* criteria. Including patients in this category when they do not meet criteria on the basis of *number* of symptoms would clarify and make consistent existing standards, aligning them with the data presented herein. Likewise this would allow for a condition parallel to the existing cyclothymic variation, namely a bipolar diagnosis which has full major depression features but subthreshold manic features. Thus, the DSM changes outlined in Option 1(B) above are simple and consistent with existing DSM conventions.

Conclusions

Data presented herein are consistent with the view of bipolar disorder as existing on a continuum with unipolar depression. These data suggest that at a minimum, the current diagnostic approach to bipolar disorder should be modified to include routine assessment of non-manic bipolar features. Exactly how this modification should take place while awaiting another edition of the DSM is not clear, because of the lack of data on utility of new approaches. A simple means of doing so would be to add an additional example to DSM BP NOS criteria which would

make this label consistent with existing examples and symmetric with cyclothymia. Consideration of a further extension of the bipolar realm, incorporating patients who have multiple non-manic markers but lack any manic symptoms at all, should await further study of their longitudinal course and response to treatment.

References

1. Plato. Statesman 262b. In: Skemp JB ed. Plato's Statesman: a Translation of the Politicus of Plato with Introductory Essays and Footnote. Routledge & Kegan, 1952.
2. Kendall R, Jablensky A. Distinguishing between the validity and utility of psychiatric diagnoses. Am J Psychiatry 2003; 160: 4–12.
3. Robins E, Guze SB. Establishment of diagnostic validity in psychiatric illness: its application to schizophrenia. Am J Psychiatry 1970; 126: 983–987.
4. Vieta E., Phillips M. Deconstructing bipolar disorder: a critical review of its diagnostic validity and a proposal for DSM-V and ICD-11. Schizophr Bull 2007; 33: 886–892.
5. First MB. Clinical utility: a prerequisite for the adoption of a dimensional approach in DSM. J Abnorm Psychol 2005; 114: 560–564.
6. Bauer M, Beaulieu S, Dunner DL, Lafer B, Kupka R. Rapid cycling bipolar disorder: diagnostic concepts. Bipolar Disord 2008; 10: 153–162.
7. MacKinnon DF, Pies R. Affective instability as rapid cycling: theoretical and clinical implications for borderline personality and bipolar spectrum disorders. Bipolar Disord 2006; 8: 1–14.
8. Craddock N, O'Donovan MC, Owen MJ. Genes for schizophrenia and bipolar disorder? Implications for psychiatric nosology. Schizophr Bull 2006; 32: 9–16.
9. Akiskal HS. Demystifying borderline personality: critique of the concept and unorthodox reflections on its natural kinship with the bipolar spectrum. Acta Psychiatr Scand 2004; 110: 401–407.
10. Paris J, Gunderson J, Weinberg I. The interface between borderline personality disorder and bipolar spectrum disorders. Compr Psychiatry 2007; 48: 145–154.
11. Gunderson JG, Weinberg I, Daversa MT et al. Descriptive and longitudinal observations on the relationship of borderline personality disorder and bipolar disorder. Am J Psychiatry 2006; 163: 1173–1178.
12. Kraepelin E. Lectures on Clinical Psychiatry, 3rd edn. New York, NY: William Wood, 1917.
13. Vieta E, Suppes T. Bipolar II disorder: arguments for and against a distinct diagnostic entity. Bipolar Disord 2008; 10: 163–178.
14. Katzow JJ, Hsu DJ, Ghaemi SN. The bipolar spectrum: a clinical perspective. Bipolar Disord 2003; 5: 436–442.
15. Dunner DL. Clinical consequences of under-recognized bipolar spectrum disorder. Bipolar Disord 2003; 5: 456–463.
16. Angst J, Cassano G. The mood spectrum: improving the diagnosis of bipolar disorder. Bipolar Disord 2005; 7 (Suppl. 4): 4–12.
17. Mondimore FM. Unipolar depression/bipolar depression: connections and controversies. Int Rev Psychiatry 2005; 17: 39–47.
18. Moller HJ, Curtis VA. The bipolar spectrum: diagnostic and pharmacologic considerations. Expert Rev Neurother 2004; 6 (Suppl. 2): S3–S8.
19. Skeppar P, Adolfsson R. Bipolar II and the bipolar spectrum. Nord J Psychiatry 2006; 60: 7–26.
20. Pies R. The historical roots of the 'bipolar spectrum': Did Aristotle anticipate Kraepelin's broad concept of manic-depression? J Affect Disord 2007; 100: 7–11.
21. Angst J. The bipolar spectrum. Brit J Psych 2007; 190: 189–191.
22. Baethge C, Salvatore P, Baldessarini RJ. Cyclothymia, a circular mood disorder. Hist Psychiatry 2003; 14 (55 part 3): 377–399.
23. Koukopoulos A. Ewald Hecker's description of cyclothymia as a cyclical mood disorder: its relevance to the modern concept of bipolar II. J Affect Disord 2003; 73: 199–205.
24. Sadler JZ. Values and Psychiatric Diagnosis. Oxford: Oxford University Press, 2005.
25. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Washington, DC: APA Press, 1994.
26. Strober M, Carlson G. Bipolar illness in adolescents with major depression: clinical, genetic, and psychopharmacologic predictors in a three- to four-year prospective follow-up investigation. Arch Gen Psychiatry 1982; 39: 549–555.
27. Akiskal HS, Walker P, Puzantian VR et al. Bipolar outcome in the course of depressive illness. Phenomenologic, familial, and pharmacologic predictors. J Affect Disord 1983; 5: 115–128.
28. Smith DJ, Harrison N, Muir W, Blackwood DH. The high prevalence of bipolar spectrum disorders in young adults with recurrent depression: toward an innovative diagnostic framework. J Affect Disord 2005; 84: 167–178.
29. Akiskal HS, Djenderedjian AM, Rosenthal RH et al. Cyclothymic disorder: validating criteria for inclusion in the bipolar affective group. Am J Psychiatry 1977; 134: 1227–1233.
30. Klerman GL. The spectrum of mania. Compr Psychiatry 1981; 22: 11–20.
31. Akiskal HS, Pinto O. The evolving bipolar spectrum. Prototypes I, II, III, and IV. Psychiatr Clin North Am 1999; 22: 517–534.
32. Dunner DL, Tay LK. Diagnostic reliability of the history of hypomania in bipolar II patients and patients with major depression. Compr Psychiatry 1993; 34: 303–307.
33. Simpson SG, McMahon FJ. Diagnostic reliability of bipolar II disorder. Arch Gen Psychiatry 2002; 59: 736–740.
34. Sneath PH. Some thoughts on bacterial classification. J Gen Microbiol 1957; 17: 184–200.
35. Benazzi F. Bipolar II disorder and major depressive disorder: continuity or discontinuity? World J Biol Psychiatry 2003; 4: 166–171.
36. Benazzi F, Akiskal HS. Refining the evaluation of bipolar II: beyond the strict SCID-CV guidelines for hypomania. J Affect Disord 2003; 73: 33–38.
37. Benazzi F. Mixed states in bipolar II disorder: should full hypomania always be required? Psychiatry Res 2004; 127: 247–257.
38. Benazzi F. Bipolar family history of the hypomanic symptoms and dimensions of mixed depression. Compr Psychiatry 2005; 46: 399–404.
39. Benazzi F. Does temperamental instability support a continuity between bipolar II disorder and major depressive disorder? Eur Psychiatry 2006; 21: 274–279.

40. Cassano GB, Frank E, Miniati M et al. Conceptual underpinnings and empirical support for the mood spectrum. Psychiatr Clin North Am 2002; 25: 699–712.
41. Fagiolini A, Dell'Osso L, Pini S et al. Validity and reliability of a new instrument for assessing mood symptomatology: the Structured Clinical Interview for Mood Spectrum (SCI-MOODS). Int J Meth Psychiatric Res 1999; 8: 75–86.
42. Mattes JA. Irritability and depression. Am J Psychiatry 2005; 162: 1025.
43. Cassano GB. Reply to Mattes. Am J Psychiatry 2005; 162: 1025.
44. Angst J. Epidemiology of the bipolar spectrum. Encephale 1995; 6: 37–42.
45. Angst J. The emerging epidemiology of hypomania and bipolar II disorder. J Affect Disord 1998; 50: 143–151.
46. Angst J, Gamma A, Benazzi F et al. Toward a re-definition of subthreshold bipolarity: epidemiology and proposed criteria for bipolar-II, minor bipolar disorders and hypomania. J Affect Disord 2003; 73: 133–146.
47. Kessler RC, Akiskal HS, Angst J et al. Prevalence and effects of mood disorders on role performance in the United States. Bipolar Disord 2005; 7 (Suppl. 2): 18.
48. Judd LL, Akiskal HS. The prevalence and disability of bipolar spectrum disorders in the US population: re-analysis of the ECA database taking into account subthreshold cases. J Affect Disord 2003; 73: 123–131.
49. Saggese JM, Lieberman DZ, Goodwin FK. The role of recurrence and cyclicity in differentiating mood disorder diagnoses. Primary Psychiatry 2006; 13: 43–48.
50. Ghaemi SN, Ko JY, Goodwin FK. 'Cade's disease' and beyond: misdiagnosis, antidepressant use, and a proposed definition for bipolar spectrum disorder. Can J Psychiatry 2002; 47: 125–134.
51. Mitchell PB, Goodwin GM, Johnson GF, Hirschfeld RMA. Diagnostic guidelines for bipolar depression: a probabilistic approach. Bipolar Disord 2008; 10: 144–152.
52. Akiskal HS, Maser JD, Zeller PJ. Switching from 'unipolar' to 'bipolar II': an 11-year prospective study of clinical and temperamental predictors in 559 patients. Arch Gen Psychiatry 1995; 52: 114–123.
53. Leonhard K. Aufteilung der Endogenen Psychosen. Berlin: Akademie-Verlag, 1957.
54. Perris C. A study of bipolar (manic-depressive) and unipolar recurrent depressive psychoses. I. Genetic investigation. Acta Psychiatr Scand Suppl 1966; 194: 15–44.
55. McGuffin P, Rijsdijk F, Andrew M, Sham P, Katz R, Cardno A. The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. Arch Gen Psychiatry 2003; 60: 497–502.
56. Kelsoe JR. Arguments for the genetic basis of the bipolar spectrum. J Affect Disord 2003; 73: 183–197.
57. Sato T, Bottlender R, Schroter A, Moller HJ. Frequency of manic symptoms during a depressive episode and unipolar 'depressive mixed state' as bipolar spectrum. Acta Psychiatr Scand 2003; 107: 268–274.
58. Akiskal HS, Benazzi F. Family history validation of the bipolar nature of depressive mixed states. J Affect Disord 2003; 73: 113–122.
59. Maj M, Pirozzi R, Magliano L, Bartoli L. Agitated depression in bipolar I disorder: prevalence, phenomenology, and outcome. Am J Psychiatry 2003; 160: 2134–2140.
60. Sato T, Bottlender R, Sievers M, Moller HJ. Evidence of depressive mixed states. Am J Psychiatry 2005; 162: 193–194.
61. Swann AC, Gerard Moeller F, Steinberg JL, Schneider L, Barratt ES, Dougherty DM. Manic symptoms and impulsivity during bipolar depressive episodes. Bipolar Disord 2007; 9: 206–212.
62. Frye MA, McElroy SL, Helleman G et al. Clinical Correlates Associated with Treatment Emergent Mania. Poster Presentation. Toronto, ON: American Psychiatric Association, 2006.
63. Ghaemi SN, Miller CJ, Berv DA, Klugman J, Rosenquist KJ, Pies RW. Sensitivity and specificity of a new Bipolar Spectrum Diagnostic Scale. J Affect Disord 2005; 84: 273–277.
64. Hirschfeld RM, Williams JB, Spitzer RL et al. Development and validation of a screening instrument for bipolar spectrum disorder: the Mood Disorder Questionnaire. Am J Psychiatry 2000; 157: 1873–1875.
65. http://www.psycheducation.org/depression/BSDS.htm (accessed 12 November 2006).
66. Phelps JR, Ghaemi SN. Improving the diagnosis of bipolar disorder: predictive value of screening tests. J Affect Disord 2006; 92: 141–148.
67. Sachs GS. Strategies for improving treatment of bipolar disorder: integration of measurement and management. Acta Psychiatr Scand Suppl 2004; 422: 7–17.
68. Saenger E. The Bipolarity Index as a Tool for Assessment and Creating Rapport: an Expert Interview with Gary Sachs, MD. Medscape Psychiatry Mental Health 2005; 10(1): http://www.medscape.com/viewarticle/542319, accessed 1/28/07.
69. Ghaemi SN, Hsu DJ, Ko JY, Baldassano CF, Kontos NJ, Goodwin FK. Bipolar spectrum disorder: a pilot study. Psychopathology 2004; 37: 222–226.
70. Patten SB. Does almost everybody suffer from a bipolar disorder? Can J Psychiatry 2006; 51: 6–8.
71. Sobo S. Mood stabilizers and mood swings: in search of a definition. Psychiatr Times 1999; 16: http://www.psychiatrictimes.com/p991036.html (accessed 13 November 2006).
72. Paris J. Borderline or bipolar? Distinguishing borderline personality disorder from bipolar spectrum disorders Harv Rev Psychiatry 2004; 12: 140–145.
73. Weibe EJ. Re: 'Cades disease' and beyond. Can J Psychiatry 2003; 48: 64.
74. Harris J. The increased diagnosis of 'juvenile bipolar disorder': what are we treating? Psychiatr Serv 2005; 56: 529–531.
75. Ghaemi SN, Hsu DJ, Soldani F, Goodwin FK. Antidepressants in bipolar disorder: the case for caution. Bipolar Disord 2003; 5: 421–433.
76. Goldberg JF. When do antidepressants worsen the course of bipolar disorder? J Psychiatr Pract 2003; 9: 181–194.
77. El-Mallakh RS, Karippot A. Use of antidepressants to treat depression in bipolar disorder. Psychiatr Serv 2002; 53: 580–584.
78. McElroy SL, Kotwal R, Kaneria R, Keck PE Jr. Antidepressants and suicidal behavior in bipolar disorder. Bipolar Disord 2006; 8: 596–617 (part 2).
79. Baldessarini RJ. A plea for integrity of the bipolar disorder concept. Bipolar Disord 2000; 2: 3–7.
80. Horvit M. Lawsuit says drug companies conned state, Dallas Star-Telegram. Posted on 20 December 2006. http://www.newsgroups-index.com/group/talk_-politics_-medicine_l481.html (accessed 16 November 2007).
81. Moynihan R, Henry D. The fight against disease mongering: generating knowledge for action. PLoS Med 2006; 3: e191.
82. Shah AA, Finucane TE. Commercial influence on psychiatric drug studies and prescribing practices. Psychiatr

Times 2006; 23: http://www.psychiatrictimes.com/showArticle.jhtml?articleId = 189401130 (accessed 16 November 2007).
83. Ghaemi SN. The newest mania: seeing disease mongering everywhere. PLoS Med 2006; 3: e319.
84. Phelps J. Confessions of a disease monger. PLoS Med 2006; 3: e314.
85. Phelps J. How is this website funded? 2006. http://www.psycheducation.org/start/Funding.htm (accessed 5 January 2006).
86. Healy D. The best hysterias: author's response to Ghaemi. PLoS Med 2006; 3: e320.
87. Westen D, Shedler J, Bradley R. A prototype approach to personality disorder diagnosis. Am J Psychiatry 2006; 163: 846–856.
88. Angst J. The course of affective disorders. II. Typology of bipolar manic-depressive illness. Arch Psychiatr Nervenkr 1978; 226: 65–73.