REVIEW ARTICLE

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The Emergence of the Bipolar Spectrum: Validation along Clinical-Epidemiologic and Familial-Genetic Lines

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ABSTRACT *~ A new paradigm of the bipolar spectrum is shaping up in the research literature and in clinical practice. It represents a partial return to the Kraepelinian broad concept of manic depression which included many recurrent depressions. Although bipolar I and bipolar II are now part of the official nomenclature of Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition (DSM-IV), the breadth of bipolarity is not represented in this manual. Old and new evidence indicate that the most common form of bipolar II is characterized by hypomanias of shorter duration than the arbitrary threshold of four days, and that cyclothymic depressions represent a prevalent variant of the bipolar II pattern. Furthermore, evidence is now compelling that hypomania in association with antidepressant treatments requires familial bipolar diathesis for bipolar disorder (bipolar III). There also exist clinical depressions superimposed on hyperthymic temperament (bipolar IV), referring to individuals with subthreshold hypomanic traits rather than episodes. Given emerging data for a population prevalence of at least 5% for a broadly conceived bipolar spectrum—and 6% for the cyclothymic temperament—the author submits that one of ten individuals in the community either has bipolar disorder, or is at risk for it. These are probably conservative estimates, because the range of clinical phenotypes and that of temperaments at risk are expanding. A provocative development is the emergence of extensive clinical and research evidence for the comorbidity of panic, social phobia, and related anxiety states with bipolar, and especially bipolar II, disorder. In addition, prevalent mixed states beyond dysphoric mania have been described, consisting of hypomanic intrusions into major depressive states. The net effect of the broadened boundaries of bipolarity is encroachment into the terrain of so-called "unipolar" anxious-depressions and of axis II cluster B. This is an evolving reformulation of the subclassification of affective disorders reviewed in this article, validated on the basis of phenomenology, epidemiology, course, family history, twin studies, and molecular genetics. These considerations have major implications for clinical practice, methodology of genetic investigations, pharmaceutical trials of putative bipolar agents in affective disorders, and public health.* PsychopharmacologyBulletin. *2007;40(4):99-115.*

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INTRODUCTION

There is much current disagreement about the boundaries of affective disorder subtypes. This is not a new phenomenon, as the debate about affective subtypes is at least 100 years old.[1] But those who hoped that classification, with the use of operational criteria as embodied in the official nomendature of the American Psychiatric Association (of which DSM-IV-TR[2] is the latest version), would clarify matters have much to be disappointed about. Major Depressive Disorder (MDD) dominates the affective disorder arena, yet it is no secret to the astute clinical observer that many so-called "major depressive" states are in reality bipolar at some level.[3,4]

DSM-IV basically adheres to the unipolar-bipolar distinction, with strong bias in favor of non-bipolar conditions. It is true that DSM-IV has formally created the categories of "bipolar II" and "bipolar NOS (not otherwise specified)" and, in principle, the entire breadth of bipolarity should be diagnosable. But this is difficult to translate into practice because the definitions of mania and hypomania are phrased in nearly identical language (except for psychosis for the former and relative lack of disability for the latter), bipolar NOS is basically left undefined, and cyclothymia is likely to be misclassified as an erratic personality disorder.[4] In brief, the entire spectrum of bipolarity in the less-than-manic range is at risk for being relegated to MDD and/or Axis-II, Cluster B. Two decades earlier, the main diagnostic errors were in favor of schizophrenia over mania,[5] but this appears to be less of a problem today.

This paper reviews evidence in favor of a broad "bipolar spectrum" beyond classic mania and DSM-IV guidelines for bipolar disorder, linked together by various degrees of hypomania and underlying temperamental dysregulation along cydothymic and hyperthymic lines.[6–9] Since much of the research in the enlargement of the boundaries of bipolar disorder has come through the work of the present author and his collaborators, the bibliography of this article reflects key references from this work. The more extensive literature on the subject can be found in recent reviews by the author,[4,8] as well as in a monograph that has just been published as a special issue of the *Journal of Affective Disorders*.[10]

In this article, I will first trace the historical roots of the broad concept of bipolarity, and then present validating principles along epidemiologic, clinical, and familial-genetic lines.

HISTORICAL ORIGINS

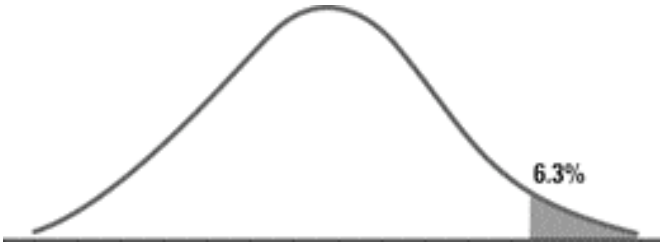
A brief review of the historical background of the development of the concepts of affective illness and personality disorders may point to the sources of our current confusion, and could thereby suggest how a new order might emerge from insights that classical observers in psychiatry have provided us.[11]

Kraepelin[12] subsumed much of what today we call mood disorders (including recurrent depressions) under the rubric of "manic-depression." He observed that many depressed patients, when followed longitudinally, developed hypomania or mania while other depressives had a family history for manic-depressive psychosis. He further noted that just as depressive symptoms could occur during mania, hypomanic intrusions into depressive episodes did occur in a considerable number of patients. These were Kraepelin's categories for mixed states, more broadly defined than in the present official diagnostic schema of DSM-IV. More importantly, Kraepelin believed that constitutionally determined personal dispositions—which today we call "temperament"—represent the fundamental states from which different affective states arose. Kraepelin's conceptualization involved affective dysregulation, which he believed generated a multitude of clinical pictures including acute confusional psychoses, acute and chronic manic states, retarded depressions, depressions which switched to brief elations, agitated melancholias, anxious-depressive mania, depression with flight of ideas, and other affective states with mood lability in continuum with normality.

Kraepelin's approach was further developed by Kretschmer,[13] who expressed the view that "endogenous psychoses are nothing but exaggerated forms of temperament." He believed that there was a central cyclothymic disposition which, in some individuals, manifested in irritable or depressive attributes, and in others, in hypomanic attributes. His formulation has a very modern ring to it: As modern molecular genetics is concerned with oligogenic traits, the high prevalence of affective traits with near-normal distribution in the community[14] is of great theoretical, genetic, and preventive significance; Figure 1 diagrams the percentage of subjects with extreme cydothymic traits based on z-score higher than the second standard deviation.

FIGURE 1

THE PERCENTAGE OF SUBJECTS WITH A Z-SCORE HIGHER THAN THE SECOND POSITIVE STANDARD DEVIATION ON THE CYCLOTHYMIC SCALE



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Another German psychiatrist, Kurt Schneider,[15] who had a profound influence on the field through his writings on what he termed "psychopathic personality" (abnormal personality in today's parlance), believed that such dispositions as the depressive, labile, and hyperthymic had little to do with the "cydothymic" disorders (his term for manic-depression). Schneider's position is similar to the one taken by DSM-IV, namelythat abnormal personalities are distinct from what we today term "bipolar disorder."

Although Schneider's descriptions of individual personality types are phenomenologically superb (we have used them in our operational definitions of the affective temperaments),[6] his legacy—to the extent it is reflected in DSM-IV—is confusing. The DSM-IV schema, also derives from psychodynamic thinking. In this schema, patients presenting with unmistakable affective signs and symptoms, instead of being considered cyclothymic, would receive such labels as "psychopathic," "histrionic" or "borderline". Likewise, patients with double depression could receive personality characterization as "passive," "avoidant," or "obsessoid," rather than being considered "depressive" in temperament. The main problem with the DSM-IV conceptualization is that patients today are at risk of being considered character-flawed rather than having constitutionally-based affective disorders. The net effect of the current conceptualization of axis II on psychiatric practice is to discourage diagnosis of affective illness in those with significant interpersonal dysfunction, thereby limiting major mood disorders to relatively straightforward periodic or cyclic cases.

THE ROLE OF TEMPERAMENT IN BIPOLARITY

Twenty-five years of clinical research, based on longitudinal observations of patients in the setting of mood clinics,[16] indicates that a subclassification based on temperament greatly clarifies the vast terrain of what some people consider personality-disordered depression, but which I prefer to consider "soft bipolar disorders."[6] Temperament is natural to the language of mood disorders as it refers to emotionality, reactivity or lack thereof, impulse control, shifts in energy level, and circadian changes. Much of what is considered in the psychosocial literature as high or low "expressed emotion" and the related construct of hypercritical attitudes reflects a clash between the temperament of the patient and that of significant others. In brief, temperament as a construct appears proximal to the chain of the charged emotional atmosphere and the resultant personal adversity which define the psychosocial context of affective disorders. I submit that temperament has a fundamental role in helping us not only in the classification of affective subtypes, but also in understanding their evolution and complications.

How does temperament shed light on the spectrum of bipolarity beyond classic mania? In essence, my thesis is that a great many depressions are bipolar by virtue of temperament.[3,5–7,9] Indeed, progression from temperament to full blown episodes has been shown in prospective follow-up of the offspring and kin of manic-depressive probands.[17]

DESCRIPTION OF THE BIPOLAR SPECTRUM

As shown in Table 1, there exists Bipolar types I, II, III, and IV, and as one would expect in a spectrum, Bipolar types _, I_, II_, III_.[3] The spectrum includes manic-depressive (bipolar-I), bipolar-II, bipolar III, and hyperthymic depressive (type IV) prototypes. These are proposed as "categorical" phenotypes, suitable for genetic investigations. However, as expected in a spectrum conceptual framework, intermediary phenotypes are encountered in clinical practice. For instance, Bipolar type_, or schizobipolar (between schizophrenia and bipolar I), Bipolar type I_, or depressions with protracted hypomania (between bipolar I and II), and Bipolar type II_ or cyclothymic depressions (between bipolar II and bipolar III). The main characteristics of each of these conditions within the spectrum follows.

Bipolar I

This is classically defined by the presence of mania that is often of psychotic proportions. There are those (mostly male) characterized with a predominant manic course, many of whom have a hyperthymic temperament.[18] Our research has shown that those who suffer dysphoric manic episodes are characterized by the intrusion of a depressive temperament (more prevalent in women) into a manic episode.[18,19] I dassify as bipolar I_ patients as those whose illness is characterized by frequent depressive episodes, and few protracted hypomanic episodes lasting

TABLE 1

THE EVOLVING SPECTRUM OF BIPOLAR DISORDERS

Bipolar _:	Schizobipolar disorder
Bipolar I:	Manic-depressive illness
Bipolar I_:	Depression with protracted hypomania
Bipolar II:	Depression with spontaneous discrete hypomanic episodes
Bipolar II_:	Depression superimposed on cyclothymic temperament
Bipolar III:	Repeated depression plus hypomania occurring solely in association with antidepressant or other somatic treatment
Bipolar III_:	Repeated hypomania occurring in the context of substance and/or alcohol (ab)use
Bipolar IV:	Depression superimposed on a hyperthymic temperament

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weeks but without developing psychotic symptoms and marked social disruption; I hypothesize that these patients are genotypically most closely linked to bipolar I patients.

Bipolar II

This type was delineated in the pioneering study by Dunner et al. at the National Institute of Mental Health (NIMH).[20] The hallmark here is recurrent anergic depression with hypomania that often occurs at the tail end of a depression. Onset and offset are abrupt, as are shifts into hypomania: the patient might go to sleep depressed and switch to hypomania in the early morning hours. These are "sunny" bipolar II's[21] with infrequent episodes, who often benefit from adaptive hypomanic periods characterized by cheerfulness and jocularity, gregariousness and people-seeking, increased sexual drive and behavior, talkativeness and eloquence, confidence and optimism, disinhibition and carefree attitudes, reduced sleep need, eutonia and vitality, and over-involvement in new projects. These manifestations of hypomania are more clearly separable from mania than the nondescript list of hypomanic signs and symptoms in DSM-IV. Hypomania in these patients occurs in discrete episodes that represent changes from the patient's baseline. Such patients are more likely to conform to the narrow (DSM-IV) concept of bipolar II with hypomania for four days or more.

However, research conducted in Memphis dating to the late 1970s,[22] and more recent epidemiological research in Zurich,[23] have demonstrated that the modal duration of hypomania is two days (rather than the four-day arbitrary threshold of DSM-IV). In collaboration with Benazzi,[24] and based on a private practice sample in Ravenna, Italy, we have reported that in nearly 90% of bipolar II, the duration of hypomania is two days or more. A Trans-Atlantic consensus statement[8] from centers specializing in bipolarity concluded that for a first episode depression it would be best to use the more conservative hypomania cutoff of four days or more, but that in most others with recurrent depression, the two or more days of hypomania cutoff was more appropriate. It is noteworthy that the Research Diagnostic Criteria defined a floor duration of hypomania of two days and a more strict duration of seven days, which in the just published NIMH collaborative study on the course of Bipolar II were shown to be indistinguishable in most parameters related to bipolarity,[25] supporting the inclusion of brief hypomanias within the bipolar spectrum.

Bipolar II_ seems to represent the more unstable ("darker") side of a putative bipolar II genotype with high recurrence of both depression and irritable hypomania superimposed upon an inter-episodic cyclothymic temperament.[21] Here, the mood dysregulation is more severe than in

ordinary bipolar II, such that affective states and temperament are not easily discriminable; hence the roller-coaster course for both patient and significant others, which in the DSM-IV schema can be mistaken for or labeled as "borderline personality." A prospective study conducted by us within the framework of the NIMH collaborative study[26] has demonstrated that cydothymic mood lability is the best predictor of which clinical depressed patients will switch into bipolar II. Also, in Italian collaboration with Savino[27] and Perugi,[28] we have shown that both panic and social phobic states commonly occur in the context of cydothymic depressions. Such patients also tend to be suicidal.[29] Finally, in support for the foregoing clinical observations, a team of researchers from the Johns Hopkins University[30] has shown that panic attacks with bipolar II disorder might represent a specific genetic subtype of bipolar disorder.

Bipolar III

In these patients, hypomania becomes evident during pharmacotherapy with antidepressants (also other somatic treatments such as phototherapy, sleep deprivation and ECT). Typically, such hypomania is brief and exhibits a low rate of recurrence. Studies conducted in collaboration with my Memphis colleagues during the early 1980s,[31] and more recently with French collaboration in the EPIDEP study,[32] indicate that these individuals are temperamentally depressive or dysthymic, often conforming to the double depressive pattern, yet give evidence for bipolar family history. This is not to say that all double depressions are bipolar, but familial bipolarity represents a clinical marker for predicting which patients with dysthymic or depressive temperament will experience brief reversible switches into hypomania.

In Bipolar III_ patients, periods of excitement and depression are so closely linked with substance and alcohol abuse that it is not easy to decide whether these periods would have occurred in the absence of such abuse.[22] The occurrence of frequent affective shifts over many years in these patients is the key to differential diagnosis, especially if family history is positive for bipolar affective disorder. Research in this interface of bipolarity and stimulant and alcohol abuse is sorely needed. It is of great relevance for genetics and public health. Their tentative inclusion in the soft bipolar spectrum opens therapeutic opportunities for a very large universe of patients with "comorbid" bipolar and stimulant-alcohol features.

Bipolar IV

This category includes depressive states superimposed on a hyperthymic temperament. Familial bipolarity supports their inclusion in the bipolar spectrum.[9] The prototypical presentation is that of a late onset

(>50 years), anergic depressive episode necessitating multiple brief courses of antidepressants (none of which work beyond a few months), and subsequent development of an excited ("agitated") depressive mixed state with psychomotor restlessness, racing thoughts, and/or intense sexual excitement.[6,7] History will often reveal that these individuals were extremely successful executives (usually male) with lifelong drive, ambition, high energy, confidence, and extroverted interpersonal skills. Unlike bipolar II, these hypomanic features do not occur as isolated brief episodes, but constitute the stable temperamental baseline of these hyperthymic depressions. I submit that it is this intrusion of an "unwelcome" depression into a hyperthymic temperament that gives rise to the mixed state. Clinically, this is an extremely dangerous condition because hyperthymic individuals are intolerant of any degree of depression, and certainly poorly tolerate the affective dysfunction associated with a depressive mixed state. Many mysteries about suicide, and suicides that one reads about in the newspaper (ie, "an extremely successful and happy person, who had everything, put the gun in his mouth") may well belong to this category. These patients might be considered "narcissistic" in the DSM-IV Axis-II schema, but are better characterized as hyperthymic with the following lifelong traits: upbeat and exuberant, articulate and jocular, overoptimistic and carefree, overconfident and boastful, high energy level, full of plans and improvident activities, versatile with broad interests, overinvolved and meddlesome, uninhibited and risk-taking, and an habitual short sleeper.

Thus far, I have documented a spectrum of affective manifestations with muted manic manifestations which merge into temperament. I have provided the justification for their inclusion within a broad bipolar spectrum beyond classic bipolar I. In our current nomenclature, because of lack of explicit characterization, many of these patients are likely to be considered "unipolar," "borderline," "substance-induced," or "psychopathic."[22,33] Instead, I have argued that their depressions are, in dinical reality, pseudo-unipolar.[5] Although in referring to the muted, less-than-manic bipolar manifestations, we have employed the terminology of "soft bipolar,"[6] types II through IV have actually received considerable "hard" research support.[4,10]

Other Putative Bipolar Spectrum Conditions

There probably also exist conditions beyond the spectrum outlined here which are part of the broader bipolar terrain (ie, beyond type IV). Both the late Klerman[34] and, more recently Noble Endicott,[35] have written about these far outreaches of bipolarity. In our clinical experience,[3] they include atypical and seasonal depressions without discernible hypomanic states, but which exhibit periodicity. Some bulimic states might represent a

variant from this seasonal pattern; other patients may present with episodic obsessive-compulsive symptoms, periodic states of irritability or acute suicidal crises in the absence of a fully defined affective syndrome. Many paraphilias and so-called "sexual addictions" with periodic exacerbations are also at some level bipolar; perhaps related to these are other impulse-controlled disorders such as gambling.[36] Finally, there are patients with episodic neurasthenic or sleep complaints, and those with non-menstrually related recurrent brief depressions.[3] This is not an exhaustive list, but conditions that should be further studied as putative bipolar variants. Their relationship to bipolar disorder is not presently established.

It is beyond the scope of this paper to discuss the complex interplay of attention-deficit hyperactivity disorder (ADHD) and juvenile bipolarity. According to some authorities, one pathway to juvenile bipolar disorder is childhood hyperactivity. This is not to say that childhood hyperactivity is an obligatory precursor of bipolar disorder—nor that all cases of ADHD are bipolar—but to suggest that up to a third of juvenile onsets of bipolar disorder give history of some form of "hyperactivity" prior to the more overt bipolar manifestations. The interested reader may refer to the work of Biederman and colleagues at Harvard.[37] Here again, the proposed link of ADHD and bipolar spectrum disorders is tentative and in need of further investigation.

The concept of the "Bipolar Spectrum" is a hot topic in both clinical psychiatry and in research into the genetic origins of bipolar disorder. The author has elsewhere[8,9] presented the thesis that broad concepts of bipolarity help in identifying patients on the border of bipolar disorder who might be de-stabilized by antidepressants and could potentially benefit from therapeutic interventions developed for dassical bipolar disorder. As far as genetic investigations, some authorities believe that it would be easier to identify the molecular basis of the illness by focusing on the "hard core" euphoric manic phenotype,[38] while others contend that the most prevalent expressions of bipolar disorder belong to a "soft spectrum," the inclusion of which in genetic investigations would facilitate in the discovery of the oligogenic basis for bipolarity.[8] A recent commentary by Baldessarini[39] has critiqued the broadening of the concept of bipolar disorder on methodological grounds, fearing that the dilution of the classical concept would introduce too much heterogeneity to be manageable in research. It is nonetheless noteworthy that essentially all authors cited by Baldessarini throughout history who have described the phenomenology of this illness from Aretaeus to the present author have proposed broad concepts of bipolarity. Angst, one of the authors cited and a staunch advocate of the unipolar-bipolar distinction, has recently endorsed the broadest view of bipolarity.[40]

At the heart of the above debate is whether the soft expressions of bipolar disorder can be reliably identified in epidemiologic and clinical populations, and once identified, what strategies should be used to validate them. This is obviously a new area of investigation and support in its favor is presently strongest for types I through III.[8,10]

EPIDEMIOLOGIC CONSIDERATIONS

A good starting point for validation of a spectrum concept is prevalence in the general population. The dassical figure of 1% for bipolar disorder has been challenged by studies (Table 2) during the last few years which have reported much higher rates in the community[8,40–42] We will focus on three of these studies. Angst's most recent figure for clinical bipolarity is 10.9%,[40] a rate which is based on the broadest definition of bipolarity in a relatively small sample size in the canton of Zurich. Judd and Akiskal,[41] also using a broad redefinition of bipolarity, but using a more representative US National ECA database, have reported a figure of 6.4%. The study by Hirschfeld et al.,[42] based on a self-rated questionnaire that is most relevant to the classic end of the spectrum, reported a community prevalence of 3.7%. The various studies summarized in Table 2 suggest a modal figure of 5%.

The definition of bipolar II in the foregoing studies deviates from that in DSM-IV, which is based on a hypomania threshold of four or more days. As discussed earlier, there is now substantial evidence[8] that depressions with hypomania of two or more days belong to the bipolar spectrum. The validation of the two day threshold is based on age at onset, rate of depressive recurrence, rates of atypical depressive features and, most importantly, bipolar family history. The varying rates of bipolarity in the population are largely due to the varying definitions of bipolar II and related subthreshold bipolar conditions.

TABLE 2

CONVENTIONAL AND EMERGING DATA ON LIFETIME PREVALENCE RATES OF BIPOLAR DISORDER IN REPRESENTATIVE LARGE NATIONAL OR REGIONAL SAMPLES

AUTHOR (YEAR/COUNTRY)	JOURNAL	RATE (%)
Regier et al. (1988/USA)	Arch Gen Psychiatry	1.3
Kessler et al. (1994/USA)	Arch Gen Psychiatry	1.6
Lewinsohn et al. (1995/USA)	J Am Acad Child Adolesc Psychiatry	5.7
Weissman et al. (1996/cross-national)	JAMA	0.3–1.5
Szadoszky et al. (1998/Hungary)	J Affect Disord	5.0
Angst et al. (1998/Switzerland)	J Affect Disord	8.3
Judd and Akiskal (2003/USA)	J Affect Disord	6.34
Hirschfeld et al. (2003/USA)	J Clin Psychiatry	3.7

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How about clinical populations? There is now converging data from many studies both in the US and Europe which indicate that 30–70% of patients presenting with major depressive episodes meet criteria for bipolar II.[8] The systematic French national study EPIDEP has the virtue of reporting national data from four different regions of France, in which 40% of major depressives were diagnosed as bipolar II.[43]

As far as studies on sub-clinical bipolar temperaments, the best data derives from an Italian national study of "clinically-well" students,[14] which have revealed a relatively high prevalence of those with extreme scores (based on z-scores higher than 2 standard deviations) on such trait measures as cyclothymia (6.3%), depressiveness (3.6%), and irritable temperament (2.2%). Cyclothymia is the most validated temperament whose relevance to bipolar disorder is validated by prospective follow-up and family history[22] If we add the cydothymia rate of 6.3% in a student population[14] to the model figures of 5% for the clinical variants within the spectrum,[8] we obtain an estimated population rate of 10–11% for the bipolar trait (nearly identical to the broad figure reported by Angst et al.).[40] The foregoing considerations suggest that bipolar disorder extends from the relatively uncommon severe psychotic disorder to a highly prevalent cyclothymic disposition that is sub-clinical.

GENETIC CONSIDERATIONS

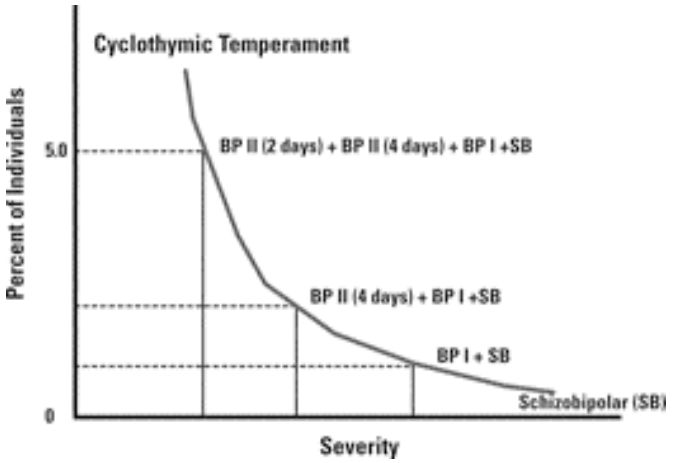
In family studies of bipolar disorder the most common phenotype in first-degree family members is depression.[44] Adoption studies have demonstrated that the biological kin of patients with bipolar disorder raised by parents without affective illness, exhibit milder and "neurotic" forms of depression.[45] Most importantly, monozygotic co-twins of manic-depressant patients are not only concordant for the strict phenotype of the illness, but they also exhibit an excess of schizophreniform psychoses, as well as "moody persons."[46] Such data suggests that the genotype of the illness extends from extremely psychotic mania that requires hospitalization to temperamental dysregulation that remains largely ambulatory and untreated.

Molecular genetic studies have also shown some overlap between schizophrenia and bipolar disorder,[47,48] and another study has shown overlap between bipolar II and panic disorder.[30] These provocative data suggest that the dysregulation in bipolar disorder extends beyond mood disturbance in the narrow sense, to include activation into psychosis, and even broader affective dysregulation which subsumes anxiety states.[49] Excellent theoretical discussion on putative oligogenic contributions to bipolarity can be seen in reviews by Gershon[50] and Kelsoe.[51]

Placing epidemiologic and genetic considerations into graphic representation (Figure 2) provides us with a model of bipolar spectrum,

FIGURE 2

COMMUNITY PREVALENCE OF BIPOLAR PHENOTYPES AS A FUNCTION OF SEVERITY



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which at the one extreme subsumes relatively rare forms of schizo-bipolar and bipolar I disorders, and at the other extreme subsumes the large terrain of soft bipolarity, consisting of cyclothymia, bipolar II with two-day hypomanias; the bipolar II's with four-day hypomania occupy an intermediary position (for the sake of simplicity, we have omitted other soft phenotypes from representation in the graph).

HIGH-RISK STUDIES

In examining the juvenile offspring and first-degree kin of bipolar adults,[17] we encounter more affected cases with major depressive disorders, dysthymia and mixed states than full-blown mania. Prospective follow-up of such juvenile patients without clear-cut bipolarity often reveals transformation into bipolar II and bipolar I disorder in many, but not all offspring. Such data are best understood in a spectrum model. They have tremendous importance in preventive psychiatry. This conclusion is further buttressed by the fact that many such offspring display cyclothymic moodiness before progressing to clinical bipolarity.

CLINICAL CONSIDERATIONS

Table 3 summarizes the clinical validating principles that can be used to establish the bipolar nature of an effective condition.[52] Of these, the most important are family history, temperament, and switching. The presence of a bipolar temperament (eg, cydothymia) is an indication of an early-onset disorder, which is most often familial.[53] The evidence for the remaining

TABLE 3

CLINICAL VALIDATING PRINCIPLES FOR A PUTATIVE BIPOLAR SPECTRUM CONDITION

- Phenomenology
- Comorbidity
- Family History
- Course
- Age at onset
- Temperament
- Switching
- Cyclicity
- Mixity
- Seasonality

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principles is documented elsewhere.[4,6,8] Although still controversial, and while DSM-IV continues to deny it, there is actually extensive international evidence,[8,32] that switches into hypomania and mania occurring on anti-depressants strongly indicate a bipolar diathesis. In dinical practice, pending further clarification through follow-up, we recommend that such patients can be provisionally classified as bipolar III.

On the basis of the foregoing validating principles and an emerging literature[54,55] the following "depressive" clinical presentations should be considered as putative soft bipolar conditions: Depression + intra-episode "hypomania" (depressive mixed state); agitated depression (severe depressive mixed state); postpartum depression, especially those with psychotic features; atypical depression and/or episodic neurasthenic complaints; refractory depression (failed anti-depressant from three different classes); depression with bipolar family history (pseudo-unipolar depression); and, depression with erratic personality disorder(s). The conditions described are often misconstrued as recurrent major depressive in nature. The author submits that they have affinity to bipolar disorder, yet surprisingly they are not listed in the bipolar NOS category in DSM-IV. There is also recent evidence that anxious inhibition may partly replace the depressive phase in certain patients with hyperthymic and cyclothymic tendencies, resulting in social phobic, panic, and obsessive-compulsive variants of bipolarity;[28,56] these patients are often considered to have anxious depressions with mood instability.

It is important to consider soft bipolarity in the foregoing conditions, because such patients often respond poorly to antidepressant monotherapy. The basis for this statement is clinical experience in specialized mood and bipolar clinics,[3,57] and this is an area that would benefit from

more rigorous studies to demonstrate the efficacy of mood stabilizer augmentation in such patients. Data is also emerging form general medical settings,[58] in support for a broad spectrum of bipolar cases accounting for at least a third of all depressions in these settings.

CONCLUSION

The concept of a bipolar spectrum is a heuristic concept that is rooted in the descriptive clinical tradition, and is validated by a new wave of epidemiologic studies demonstrating the high prevalence of sub-threshold cases, familial aggregation studies, high-risk offspring studies, analysis of monozygotic "discordance," and molecular linkage studies. Family history for bipolar disorder, cyclothymic temperament, and switching on antidepressants represent the most useful validating principles in clinical practice when examining depressed patients without antecedent frank hypomania. Early age at onset, postpartum onset, mixity, high rate of recurrence, cyclicity, and seasonality can also serve as clinical validators. Specific comorbid patterns of depression with alcohol and stimulant abuse, as well as that of social phobic, panic and OCD should also raise clinical suspicion of a bipolar diathesis. The thrust of arguments made in this review suggests that the clinical management of affective disorders will not improve significantly until there is recognition that many, if not most, depressions presenting clinically are, at some level, bipolar. As counter-intuitive as this suggestion might be, there is increasing evidence in its support summarized in this paper.

This exercise in limiting unipolarity and expanding bipolarity is in the service of treatment, especially the necessity of avoiding antidepressants or antidepressant monotherapy. The art of clinically managing these patients goes much beyond anticonvulsant concoctions. It requires the art of caring for temperamentally restless—albeit charming—individuals with troubled lives. This topic cannot be covered in the space provided here, but for those who believe that a good prognosis illness has turned into a poor prognosis illness,[59] I would suggest that a major reason why this has happened is because the field of psychiatry—in the current "managed care" climate—has abandoned the mood clinics that used to provide access to sophisticated clinical care for the affectively ill and their families.[60]

I would like to sign off where I started: on the necessity of incorporating temperament into our conceptual frame of affective disorders. This is not just a terminological preference in a nosological sense. I submit that much of what goes into Axis II is pejorative to patients and generates a distance—if not countertransference—between patient and doctor. Temperament, which defines the long-term, unstable underpinnings of the affective spectrum presented here, also encompasses much of what is

positive and desirable about the person suffering from this spectrum of disorders. Temperament helps in the affective bond between patient and doctor, and thereby makes caring possible.

The positive traits of bipolar patients are even more characteristic of their first-degree relatives.[61–63] The presence of achievement, success and creativity in the "well" relatives of bipolar patients indicates that the "dilute" genotypes of the illness may have evolved to subserve adaptive functions such as exploration and risk taking. Such an evolutionary perspective[64] represents the ultimate theoretical underpinnings of the concept of bipolar spectrum. The temperaments themselves, particularly the cyclothymic and hyperthymic, may further subserve such functions as interpersonal charm and sexual selection, and territoriality. ✤

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