The Bipolar Spectrum

A Review of Current Concepts and Implications for the Management of Depression in Primary Care

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Family physicians inevitably encounter patients with bipolar disorders, often when the patient is depressed. For most of these patients, the attendant elevations in mood fall short of mania. Such milder periods of expansive mood, hypomanias, may go unrecognized unless the physician specifically queries the patient to uncover them. In addition, patients with bipolar disorders often manifest other distinctive characteristics. Understanding of these hints of bipolarity is helpful to clinicians treating depressive illness. Patients with bipolar disorders are at risk for treatment complications caused by the administration of antidepressants without the concurrent use of mood stabilizers, such as lithium carbonate, valproate sodium, and carbamazepine. Such complications include exacerbation of hypomania or mania, induction of refractory states, and, perhaps, rapid cycling or mixed states. We review current issues in classification of bipolar disorders and emphasize the importance of identifying hypomania. An introduction to the concept of affective temperaments and a brief review of treatment strategies and treatment complications are included.
bipolar illness is underestimated in these studies. Future investigations into the prevalence of affective subtypes in primary care can settle this issue, if the standardized instruments used are sufficiently sensitive for hypomania.

Aside from questions of actual prevalence, family physicians inevitably encounter patients with bipolar disease, often during a depressed episode. In most of these patients, the predominant elevations in mood fall short of mania. Without specific queries to uncover hypomania and other historical factors that are typical for bipolarity, these less obvious but more common forms of the illness will go unrecognized.

Patients with bipolar disease may be at risk for treatment complications resulting from the administration of antidepressants unless they are also taking mood stabilizers such as lithium carbonate, valproate sodium, and carbamazepine. Mania, hypomania, mixed states, rapid cycling (4 or more cycles per year), and refractory status may complicate the illness course of patients with bipolar disease who are so treated. Patients with bipolar disease are less likely than patients with unipolar disease to respond to antidepressant monotherapy. It is, therefore, necessary that family physicians be informed about the full spectrum of bipolar illness.

**HISTORICAL PERSPECTIVES**

Historical conceptualizations of depression and mania vary, yet maintain a certain overall consistency. Hippocrates was one of the first to propose the notion that depressive and manic states were the result of a disturbance of biological processes. He rejected more ancient beliefs that the illnesses represented supernatural infiltrations of the body, believing instead that the brain governed affective states and was the site of disturbances in mood. Hippocrates theorized that imbalances of certain bodily fluids influenced moods. For example, melancholy was the result of an autumnal predominance of black bile; mania, a springtime overabundance of yellow bile. Thus, Hippocrates recognized the seasonal nature of moods common to many patients with bipolar disease. The writings of Aristotle of Cappadocia also demonstrate an intimate understanding of various presentations of mania, tempers, and sudden mood switches.

Greek conceptions of mania and melancholia were broad. Mania was comparable to a condition of mad excitable behavior and included disorders such as drug intoxication. Melancholia manifested itself in protracted fear and depressed behaviors. Indeed, mania, melancholia, and phrenitis (acute organic delirium) were the only terms available to describe psychiatric illness.

Attempts to narrow the definitions of mania and melancholia did not occur until the 19th century. In this era, the use of a clinicanoanatomical view of illness, in which symptoms resulted from specific lesions, mandated precise descriptive terminology. Thus, the use of the general term depression began. At the end of the 19th century, medicine considered mania and melancholia to be disorders of affect and not intellect, occurring in persons with certain premorbid personality or temperamental traits.

Emil Kraepelin used observations of symptoms, illness course, and temperamental predisposition in his investigations. Kraepelin separated psychoses into 2 distinct groups: those of a deteriorating nature and those characterized by a preservation of function. He placed mania and depression in the latter and considered them to be alternate manifestations of the same illness. Mania became a state of the “essential morbid symptoms of flight of ideas, exalted mood and pressure of activity,” whereas melancholia or depression (he was the first to use depression as a diagnostic term) was a sad or anxious moodiness and a sluggishness of thought and action. Persons in mixed states displayed symptoms of both. Kraepelin theorized manic-depressive illness as a continuum. Mania ranged from hypomania, a state of manic excitement in which perception was not disturbed, to delirious mania, an intense mania with profound delusions, hallucinations, and serious disturbances of perception or reality testing. Depression varied from mild illness states consisting only of poverty of thought, activity, and energy to severe forms with hallucinations, delusions, and a clouding of consciousness.

Kraepelin also identified the seeds of more syndromal illness in various temperamental traits that he termed affective tempers. This concept of a manic-depressive spectrum ranging from mild temperamental involvement to more severe, even psychotic, illness is in revival in current psychiatric thinking. In American psychiatry, the term bipolar illness replaced the European designation manic-depressive. Even so, the authors of the most authoritative American text on the illness prefer the term manic-depressive, because many recurrent unipolar depressive states seem to have key elements in common with manic-depression.

**CURRENT CLASSIFICATIONS**

The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) divides bipolar illness into 4 categories based on the severity and duration of the expanded mood state. These are Bipolar I Disorder, Bipolar II Disorder, Cyclothymic Disorder, and Bipolar Disorder Not Otherwise Specified.

**BIPOLAR I**

Bipolar I Disorder (Table 1) corresponds to the classic definition of manic-depressive illness and requires a Manic Episode (Table 1) for diagnosis. Specifiers for psychotic features, catatonic features, or postpartum onset further describe the current episode. Patients with Bipolar I Disorder are often hypomanic, however, and if the most recent episode of illness is hypomanic, this is included in the diagnosis. Mixed manic or hypomanic and depressed features are often seen as well. A current manic, mixed (Table 1), or depressed episode may be described as mild, moderate, severe without psychotic features, severe with psychotic features, in partial remission,
or in full remission. If the most recent episode is one of major depression, the depression may be specified as chronic, with melancholic features, or with atypical features. Episodic patterns include with or without full recovery, seasonal (applies to the pattern of major depression only), or rapid cycling.

Criteria for mania have been offered by various sources. The DSM-IV criteria are, perhaps, the most familiar. Other descriptions exist, however, and lend additional clarity to the definition of the syndrome (Table 1).13

### BIPOLAR II

Bipolar II Disorder (Table 2) is characterized by recurrent Major Depressive Episodes and Hypomanic Episodes. It has been variously theorized as an incomplete penetration of Bipolar I Disorder or an autonomous illness that predominates in females.14 The family histories of patients with Bipolar II Disorder are usually free of manic illness.15,16 In addition, only 5% of patients with Bipolar II disease will eventually have Bipolar I disease.17 This supports the view of Bipolar II as being an autonomous illness.

For the DSM-IV diagnosis of Bipolar II, hypomania (Table 2) of 4 days’ duration is required, and the expanded mood state must be objectively verified as different or distinct from usual functioning. Specifiers are similar to those for Bipolar I, except that hypomania is by definition never psychotic and only a current major depressive may be specified as having psychotic features.

### CYCLOTHYMIC DISORDER

Cyclothymic Disorder (Table 3) is a cyclic mood disorder differentiated from Bipolar II Disorder by the failure of depressed episodes to meet the criteria for major depression. It is an unstable diagnosis because Bipolar I or II Disorder will eventually develop in 15% to 50% of those with Cyclothymic Disorder.12

### BIPOLAR DISORDER NOT OTHERWISE SPECIFIED

Bipolar Disorder Not Otherwise Specified is a residual category of illness encompassing mood disorders determined by the clinician to exist in the bipolar realm, but not meeting criteria for another bipolar disorder. Examples of Bipolar Disorder Not Otherwise Specified are periods of expanded mood that did not meet the 4-day–duration criterion for hypomania, recurrent Hypomanic Episodes without episodes of depression, or periods of expanded mood that fulfill these criteria but cannot be independently verified or are not noticeable by others.

### ORGANIC CAUSES

Certain general medical conditions and treatments may mimic mania or hypomania. Phencyclidine hydrochloride, cocaine, and other illicit stimulants produce excited states. Isoniazid, levodopa, corticosteroids, and sympathomimetic amines also can induce similar symptoms. Other causes of secondary mania include metabolic disturbances such as chronic adrenocortical insufficiency, Cushing disease, hyperthyroidism, and hypothyroidism. narrowed...
Table 2. Bipolar II Disorders

Criteria for Bipolar II Disorder*
A. One or more major depressive episodes or has been present.
B. At least 1 hypomanic episode occurs or has been present.
C. A manic episode or a mixed episode has never occurred.
D. The mood symptoms listed in criteria A and B are not better accounted for by schizoaffective disorder and are not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder not otherwise specified.
E. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Table 3. Criteria for Cyclothymic Disorder*
A. For at least 2 years, numerous periods with hypomanic symptoms and numerous periods with depressive symptoms that do not meet criteria for a major depressive episode have been present. In children and adolescents, the duration must be at least 1 year.
B. During the 2-year period (1 year in children and adolescents), the person has not been without the symptoms listed in criterion A for more than 2 months at a time.
C. No major depressive episode, manic episode, or mixed episode has been present during the first 2 years of the disturbance. After the initial 2 years (1 year in children and adolescents) of Cyclothymic Disorder, there may be superimposed manic or mixed episodes (in which case both Bipolar I Disorder and Cyclothymic Disorder may be diagnosed) or major depressive episodes (in which case Bipolar II Disorder and Cyclothymic Disorder may be diagnosed).
D. The symptoms listed in criterion A are not better accounted for by schizoaffective disorder and are not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder not otherwise specified.
E. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

*Adapted from American Psychiatric Association.12(pp362-363)
†Adapted from American Psychiatric Association.12(p356)

As noted previously, Kraepelin11 described temperaments he believed represented the substrates from which more syndromal illness developed. These descriptions have roots in the classical medical thinking of ancient Greece. Similar temperaments have been studied as predictive and modifying factors in mood disorders.1,3,13 Criteria for the temperaments are based on neurovegetative and psychological determinants. These temperaments are important in the recognition and management of mood disorders.

The affective temperaments are defined generally as subaffective (symptomatically nonimpairing) “habitual traits that patients with affective syndromes exhibit—as reported by them and at least one significant other—pertaining to interepisodic and premorbid periods.”34 Affective temperaments describe traits that precede and endure the more symptomatic periods of illness themselves.19,21 They overlap premorbid personality and affective episodes and can be thought of as “mild to moderate manifestations of illness assumed to be intricately bound up with the genetic predisposition to mania and depression.”

Current psychiatric literature describes the following 4 specific temperaments: hyperthymic, dysthymic, cyclothymic, and irritable. There is overlap between the temperaments, and Kretschmer,22 in particular, emphasized the observable blendings and overlap in his term cycloid personality.

HYPERTHYMIC TEMPERAMENT

The hyperthymic temperament (Table 4), with its Greco-Roman equivalent, the sanguine temperament, is the temperament of many entrepreneurs and other highly successful people who seem almost superhuman in their ability to create, coordinate, and participate. They are described by Kraepelin11(pp129-130) as the “manic” temperament:
Brilliant, but unevenly gifted personalities... they charm us by their intellectual mobility, their versatility, their wealth of ideas, their ready accessibility and their delight in adventure, their artistic capability, their good nature, their chery, sunny mood. But at the same time they put us in an uncomfortable state... by a certain restlessness, talkativeness... excessive need for social life, capricious temper... lack of reliability, steadiness, and perseverance in work, a tendency to building castles in the air and scheming...

These persons disown negative affects, are not inclined to introspection, and are impulsive, action-oriented risk takers.20 Their “natural grandiosity” and denial make them infrequent visitors to medical caregivers unless more symptomatic and long lasting depressive episodes begin to occur. With hyperthymic men this can be seen as a burnout in middle or later life. In hyperthymic women, the hormonal climacterics, particularly postpartum periods, become times of increased vulnerability for degeneration of the temperament into more syndromal affective illness. However, if the premorbid temperamental hypomanic features (and thus the bipolarity) are ignored, these men and women may be subjected to trials with antidepressant agents without the protection of anticycling agents such as lithium carbonate, valproate sodium, or carbamazepine.1 In this situation, mania, hypomania, rapid cycling, mixed hypomaniac-depressed states, and refractory illness may be the unfortunate result.

**DYSTHYMIC TEMPERAMENT**

Like Eeyore the donkey of A. A. Milne’s Winnie the Pooh stories, those with dysthyMIC temperament (Table 4) view the world through gray spectacles. They are the proverbial “half-empty glass” class. Their introversion often creates an atmosphere of social phobia, and the tendency to be guilt-ridden makes them conscientious, loyal, and, therefore, desirable employees. This proclivity toward a work orientation may strain relationships already made tenuous by the anergia and passivity integral to the temperament. Kraepelin111(p120) writes:...

...From youth up there exists in the patients a special susceptibility for the cares, the difficulties, the disappointments of life... in every occurrence feel the small disagreeables much more strongly than the elevating and satisfying aspects. ... Every task stands in front of them like a mountain; life with its activity is a burden which they habitually bear.

**CYCLOTHYMIC TEMPERAMENT**

People who manifest a chronic pattern of alternating (biphasic) subaffective features comprise the cyclothymic temperament (Table 4), which occurs in about 6% of the population.2223 They spend several days in each phase and little time in a more stable or euthymic pattern. The positive phase consists of neurovegetative and behavioral symptom clusters similar to hypomania, such as talkativeness, cheerfulness, and exuberance, with a decreased requirement for sleep. The negative phase is more reminiscent of the dysthyMIC temperament, which includes symptoms such as gloominess, pessimism, sensitivity, and introversion, with a tendency to

### Table 4. Criteria for Affective Temperaments*

<table>
<thead>
<tr>
<th><strong>Hyperthymic Temperament</strong></th>
<th><strong>DysthyMIC Temperament</strong></th>
<th><strong>Cyclothymic Temperament</strong></th>
<th><strong>Irritable Temperament</strong></th>
</tr>
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<tbody>
<tr>
<td>1. Indeterminant early onset (younger than 21 y)</td>
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<tr>
<td>2. Excessive use of denial as an ego defense</td>
<td>2. Given to worry</td>
<td>2. Intermittent short cycles with infrequent euthymia</td>
<td>2. Tendency to brood</td>
</tr>
<tr>
<td>5. Intermittent subsyndromal hypomanic features with infrequent intervening euthymia</td>
<td>5. Skeptical, hypercritical, or complaining</td>
<td>5. Habitually moody, irritable and choleric, with infrequent euthymia</td>
<td>5. Early onset (younger than 21 years)</td>
</tr>
<tr>
<td>7. Cheerful, overoptimistic, or exuberant</td>
<td>7. Periods of mental confusion and apathy alternating with periods of sharpened and creative thinking</td>
<td>7. Overtalkative and jocular</td>
<td>7. Impulsive</td>
</tr>
<tr>
<td>8. Warm, people-seeking, and extraverted</td>
<td>8. Conscientious or self-disciplining</td>
<td>8. Habitual short sleeper (&lt;6 h/d, including weekends)</td>
<td>8. Impulsive</td>
</tr>
<tr>
<td>9. High energy level and full of improvisive activities</td>
<td>9. Habitual hyponomolence (≥9 h/d)</td>
<td>9. Habitual hypersomnolence (&lt;6 h/d)</td>
<td>9. Habitual hypersomnolence (&lt;6 h/d)</td>
</tr>
<tr>
<td>10. Uninhibited, stimulus seeking, or promiscuous</td>
<td>10. Tendency to brooding, anhedonia, and psychomotor inertia (all worse in the morning)</td>
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</tr>
<tr>
<td>11. Habitual short sleeper (&lt;6 h/d, including weekends)</td>
<td>11. Preoccupied with inadequacy, failure, and negativity to the point of morbid enjoyment of one’s failure</td>
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</table>

*Adapted from Akiskal and Mallya.7

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oversleep. This temperamental pattern is unstable not only in its biphasic characteristics, but also in the resulting social and interpersonal disturbances and in an established vulnerability to progression to a more syndromal mood disorder, often Bipolar II Disorder. These persons may become irritable and explosive and are typically quite “reactive” in their affect, often in an exaggerated way. This reactivity has led some to view these characteristics under Axis II personality constructs, such as Cluster B personality disorders (borderline, histrionic, narcissistic, and antisocial). However, Borderline Personality Disorder is described largely in affective language, and studies of the family pedigrees and longitudinal course in many persons with borderline personality disorders reveal a strong link to bipolar illness.

IRRITABLE TEMPERAMENT

Less common than the cyclothymic temperament is the irritable temperament (Table 4). It corresponds to the choleric temperament of Hippocrates. Choleric persons are habitually moody, brooding, and hypercritical (much like those with dysthymic temperament), but with an admixture of restless energy. It can be conceptualized as a concurrent blend of the hyperthymic and dysthymic temperaments (subsyndromal mixed state) and may complicate the cyclothymic temperamental pattern.

SUMMARY

The affective temperaments represent attenuated or subaffective forms of mood dysregulation not severe enough to be diagnosed as a formal mood disorder, but affecting individual lives through the social and demographic consequences of decisions made under the influence of these habitual traits. Clearly, syndromal illness does not develop in all affectively tempered persons. However, these temperaments identify persons most at risk for the development of more severe mood disorders, principally in the bipolar spectrum, stretching as a continuum from the subaffective temperaments to Bipolar I Illness. When distressed, impaired, or disabled patients have these premorbid or interepisodic characteristics when they seek treatment, the astute clinician will be wary of the potential implications for diagnosis and management—somatically and psychotherapeutically.

Table 5. Detecting Hypomania

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<table>
<thead>
<tr>
<th>Characteristics of Hypomania*</th>
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<tr>
<td>1. No adequate cause or grossly disproportionate to the situation</td>
</tr>
<tr>
<td>2. Labile, appearing and disappearing suddenly (bipolar “switch”)</td>
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<tr>
<td>3. Can be dysphoric in drivenness, although mood is typically elated</td>
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<tr>
<td>4. May lead to substance abuse</td>
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<td>5. Tends to impair social judgment</td>
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<td>6. Typically preceded or followed by retarded depression</td>
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<td>7. A recurrent condition</td>
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<tr>
<td>8. If the typical features are present, 48 hours’ duration sufficient to make diagnosis</td>
</tr>
<tr>
<td>9. Not psychotic</td>
</tr>
</tbody>
</table>

Suggested Questions for Uncovering Hypomania

1. Do you have days of energy or ideas that come and go abruptly?
2. On those days of energy, are you productive? Creative? Feel unconquerable?
4. Distinctly more social? Irritable?
5. Do others notice the change in your mood or energy level?
6. During these “up” times, do you do things that you later regret? Make plans you find impossible to follow through with? Take on tasks that you later suddenly lose interest in or find you are without the energy or desire to complete?
7. Are you particularly more depressed or lethargic immediately before or immediately following the cessation of these periods of energy? Does it feel like you “crash”? Does your body seem as if it is made of lead? Do you need excessive sleep?

*Adapted from Akiskal and Mallya.7

Queries aimed at the identification of the salient features of the hypomanic syndrome are an essential clinical task in the examination of every patient exhibiting a mood disorder. The features of hypomania are often subtle and inappropriately assigned to the realm of normal happiness or joy (Table 5). Patients and clinicians often see these periods of hypomania in entirely positive light (few see a doctor when they feel well) and do not connect these elevations in mood to the more severe hypersomnic and retarded depressions that often precede or follow the hypomania. Patients often adapt to these elevations in energy, activity, and mood, using them to accomplish tasks that would be difficult or impossible when depressed. Hypomanic Episodes may occur or increase in frequency seasonally or seem related to menstrual patterns in women. Regardless of the individual patterns that are possible, hypomania is autonomous, abrupt in onset and termination, and recurrent—normal happiness is not.

When combined with the description of expanded mood and activity in the DSM-IV, these criteria paint a portrait that is recognizable by clinicians and patients. As discussed earlier, to qualify as a hypomanic period, the DSM-IV criterion requires 4 days of expanded mood with objective validations of the change in mood. The criteria developed by Akiskal7 have been validated and are included in this article, because they will increase diagnostic sensitivity. Those with hypomania of less than 4 days’ duration in cases in which the clinician has concluded that the patient has a bipolar disorder would be classified in the DSM-IV as having Bipolar Disorder Not Otherwise Specified. However, good evidence suggests that most hypomanic periods last only 1 to 3 days.8,19 This suggests that the DSM-IV criteria are insensitive to
A clinical approach to the identification of “soft” bipolar disease in a patient involves consideration of subtle indicators (Table 6). Soft bipolar illness is defined as a bipolar illness without mania. The examination of a patient with bipolar illness or, perhaps more important, in whom bipolar illness may develop, includes consideration of phenomenologic characteristics, family pedigree, longitudinal course, and treatment response. Historical data and direct clinical observation are important because Bipolar II and other disorders of the “soft” bipolar spectrum require longitudinal observation and clinician expertise to diagnose.30

**‘SOFT’ BIPOLAR DISORDER**

A clinical approach to the identification of “soft” bipolar disease in a patient involves consideration of subtle hypomania and, therefore, to the diagnosis of Bipolar II.

Those with hypomanias precipitated by the use of antidepressants constitute substance-induced mood disorders under DSM-IV criteria, although considerable disagreement exists among researchers about whether bipolar disorder is the correct diagnosis. Other researchers include antidepressant-induced hypomania under the rubric Bipolar III, along with depressions occurring in conjunction with an affective temperament, such as the hyperthymic temperament.7

Uncovering hypomania in a clinical interview can be challenging. Physicians and patients may ask: “Why should times of productivity and elation be equated with illness?” Consequently, physicians and patients often need time to nurture a therapeutic alliance that allows considered answers to very specific questions (Table 5).

**DIAGNOSTIC ISSUES**

Emphasis on the value of consultation in the diagnosis and treatment of patients with bipolar disorders is important. Subtle switches in mood or confusing family histories and treatment responses may require the help of experts to decipher. Consultation, referral, or both may be indicated for diagnostic dilemmas, patients with refractory illness, or patients suffering from more severe or chronic illness.

When considering phenomenologic characteristics (symptomatology) in the search for subtle indicators of bipolarity, a careful effort to identify spontaneous hypomania is crucial. Spontaneous hypomania identifies bipolar illness even when it is used adaptively by the patient to accomplish social, occupational, or other goal-oriented behaviors. This adaptive use of the syndrome does not invalidate its importance as a clue to affective dysregulation, and it contributes to the clinical picture of the unevenness in life pursuits often seen in patients with bipolar disorders. Temperamental traits may also be used to ascertain certain patients at risk.

Other symptomatology in bipolar depressions may also lead the clinician to suspect bipolar illness. Bipolar depressions tend to contain more hypersomnia, extreme psychomotor retardation, hyperphagia (increased appetite), and “leaden paralysis” than do unipolar depressions.7 Such retarded depressions often immediately precede or follow a period of hypomania. This pattern of symptoms has been labeled atypical in the past. Under DSM-IV criteria, the term atypical further specifies a diagnosis of major depression. However, not all atypical depressions are bipolar. The identification of atypical features is perhaps most useful when combined with other bipolar indicators, if for no other reason than to create a sense of heightened awareness in the clinician.

Seasonality is common in patients with bipolar disorders. Psychotic depressions are more common in them. Women with bipolar disorders are at a higher risk for postpartum disruptions of mood, particularly depressions. However, postpartum hypomanias and manias are also seen.

Family history, or more correctly, family pedigrees, may be of great assistance in predicting bipolar outcomes. The family pedigree features most predictive for bipolarity are an established history of bipolar illness or a lithium carbonate–responding first-degree relative. Optimally, such bipolarity is a diagnosis made by a qualified clinician treating the family member, but that is often a luxury. Data can be alternatively provided by querying patients and family members for evidence of mania or hypomania in their relatives. Such indirect information is a less reliable way of establishing a diagnosis, but discovery of disabling typical symptom patterns can be quite helpful.31 Families with loading (3 or more first-degree relatives affected) and those with 3 consecutive generations affected by mood disorders suggest a bipolar pedigree.

Bipolar illness differs from unipolar illness by the earlier age of onset for affective episodes that are usually depressive in nature and often an extension of an affective temperament. This commonly occurs as a complication of the cyclothymic temperament, in which the depressed phase of the temperamental cycle deepens in severity and lengthens. Over time, patients with bipolar disorders who begin the affective course of illness with recurrent depressions will begin to manifest hypomania that may progress to full-blown mania.

The interpretation of treatment response as an indicator of bipolar illness is more problematic from a scientific viewpoint.10 De-
pressed episodes in bipolar illness are less likely to respond to treatment with antidepressant agents alone. Indeed, antidepressant agents may complicate the course of bipolar illness. Although well-designed prospective studies are lacking, a number of investigations suggest that antidepressant agents may accelerate cycling and precipitate mania and hypomania in some patients with bipolar disorders. A general statement that hypomanic responses to antidepressant agents are evidence of bipolar illness cannot be made with certainty. However, clinicians are strongly cautioned to consider bipolar illness in clinical situations in which multiple trials of antidepressant agents are ineffective or when response to a particular antidepressant agent is erratic, uneven, or short-lived. Sudden, robust responses to antidepressant agents that occur within the first 2 weeks of therapy also arouse suspicion, particularly if they are unsustained or short-lived. Sudden, robust responses to antidepressant agents that occur within the first 2 weeks of therapy also arouse suspicion, particularly if they are unsustained or accompanied by a decreased need for sleep or lapses in judgment. The most severe adverse response possible is a mixed state. Table 6 provides a descriptive profile of the clinical symptomatology of this blending of depressed and excited states.

A study by the National Institute of Mental Health (Rockville, Md) prospectively assessed clinical and temperamental predictors associated with switching from a unipolar to a bipolar diagnosis. This study used impeccable methods to examine and follow up 559 patients with a unipolar major depressive disorder. Its findings are striking and clinically relevant. First, unipolar to Bipolar II was by far the most common “switch” that occurred, usually within 3 years of diagnosis of the major depressive disorder. Second, Bipolar II is not a mild illness. Persons suffering from this disorder had protracted illnesses of earlier onset with fewer illness-free periods than those with major depressive disorder. Third, a clear temperamental profile emerged as a predictor of eventual bipolar diagnosis. This profile combined elements of mood lability, hyperenergetic involvement in activities (physical and mental), excessive use of daydreaming or fantasy, and social anxiety. Along the lines of the more familiar descriptive language for Axis II in DSM-IV, this profile could be identified as the seemingly contradictory combination of the restless emotionality of cluster B (histrionic, narcissistic, borderline) with the introverted nevroticism of cluster C (avoidant, dependent)—a profound tendency for attention seeking, combined with an equally intense fear of being noticed or an inflated sense of self-importance coupled with chronic feelings of neediness. This unstable temperamental profile seemed more fundamental in defining Bipolar II than the Hypomonic Episodes emphasized in DSM-IV. A summary of personality factors that differentiated patients in whom a Bipolar II Disorder developed from patients in whom a unipolar diagnosis was maintained is given in Table 7.

### Table 7. Personality Factors That Differentiate Patients in Whom Bipolar I Disorders Evolved to Bipolar II (BPII) Disorders From Patients in Whom a Unipolar (UP) Diagnosis Was Maintained*

<table>
<thead>
<tr>
<th>Factor Characteristics</th>
<th>Table 7</th>
</tr>
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<tbody>
<tr>
<td><strong>Mood lability</strong> (P&lt;.001)</td>
<td>Mood often changes, happiness to sadness, without my knowing why</td>
</tr>
<tr>
<td></td>
<td>Have frequent ups and downs in mood, with and without apparent cause</td>
</tr>
<tr>
<td></td>
<td>Feelings are rather easily hurt</td>
</tr>
<tr>
<td></td>
<td>There are times when my future looks very dark</td>
</tr>
<tr>
<td></td>
<td>Ideas run through my head so that I cannot sleep</td>
</tr>
<tr>
<td></td>
<td>I rarely keep in fairly uniform spirits</td>
</tr>
<tr>
<td></td>
<td>Often find it difficult to go to sleep, thinking of what happened during the day</td>
</tr>
<tr>
<td></td>
<td>Often feel disgruntled</td>
</tr>
<tr>
<td><strong>Energy-activity</strong> (P&lt;.01)</td>
<td>Inclined to rush from one activity to another without pausing for enough rest</td>
</tr>
<tr>
<td></td>
<td>I am a horse for work, I am seldom exhausted</td>
</tr>
<tr>
<td></td>
<td>I am the kind of person who is “on the go” all of the time</td>
</tr>
<tr>
<td></td>
<td>I am able to work unusually long hours without feeling tired</td>
</tr>
<tr>
<td></td>
<td>I am often so much on the go that sooner or later I wear myself out</td>
</tr>
<tr>
<td></td>
<td>I am quick in my actions</td>
</tr>
<tr>
<td></td>
<td>Happiest when involved in a project that calls for rapid action</td>
</tr>
<tr>
<td></td>
<td>Period so full of pep that sleep did not seem necessary</td>
</tr>
<tr>
<td><strong>Daydreaming</strong> (P&lt;.01)</td>
<td>I daydream a great deal</td>
</tr>
<tr>
<td></td>
<td>Like to indulge in a reverie (daydreaming)</td>
</tr>
<tr>
<td></td>
<td>I frequently find myself in a meditative state</td>
</tr>
<tr>
<td></td>
<td>I am inclined to think about myself much of the time</td>
</tr>
<tr>
<td></td>
<td>My daydreams frequently are about things that can never come true</td>
</tr>
<tr>
<td><strong>Social anxiety</strong> (P&lt;.05)</td>
<td>It is hard for me to ask someone for a favor</td>
</tr>
<tr>
<td></td>
<td>When I meet new people, am afraid that I won’t do the right thing</td>
</tr>
<tr>
<td></td>
<td>Feel that I never really get all that I need from people</td>
</tr>
<tr>
<td></td>
<td>Don’t like to buy clothes for myself</td>
</tr>
<tr>
<td></td>
<td>Would rather stay free of involvements than risk disappointments</td>
</tr>
<tr>
<td></td>
<td>While in trains, buses, etc, I rarely talk to strangers</td>
</tr>
<tr>
<td></td>
<td>Hope only brings disappointment</td>
</tr>
<tr>
<td></td>
<td>I am inclined to be shy in the presence of the opposite sex</td>
</tr>
</tbody>
</table>

*Adapted from Akiskal et al. Based on factor analysis and analysis of variance on factor scores, covarying for age and sex. All P values show the significance of evolution of BPII vs maintenance of a UP diagnosis.
depends on the presence of mixed elated and dysphoric symptoms, rapid cycling, or resistance to an initial medication. Lithium carbonate is a first-line treatment for classic euphoric mania when no medical contraindications exist for its use. Valproate sodium is an effective alternative. For the patient experiencing rapid cycling, a mixture of depressed symptoms with the expanded mood (even the presence of subtle depressed symptoms), or a distinctly irritable or dysphoric mood, valproate sodium becomes the first choice in mood stabilizers. For treatment-resistant situations, prescriptions may be switched or medications combined for optimum results.

Depressive episodes are often treated with antidepressants, but close monitoring is indicated to assess for acceleration of hypomania or mania and the possible induction of rapid cycling or mixed states. Bupropion hydrochloride or a seroton reuptake inhibitor are first choices. Tricyclic antidepressants are the antidepressants most likely to accelerate expanded moods and complicate treatment. As in unipolar depression, adequate dosing and duration of treatment are essential. Treatment resistance may be overcome by augmentation with lithium carbonate,32 switching antidepressant classes, adding psychotherapy, or adding psychotherapy.

An expert consensus panel published its recommendations on the treatment of bipolar disorder.33 These recommendations are available on the Internet at www.psychguides.com. A primary care version of the guidelines is anticipated, but the current document is an excellent starting place for any physician treating bipolar disorder.

Patients suffering from bipolar illness are examined and treated in primary care settings, perhaps more frequently than is generally realized or expected based on prevalence data gathered by structured diagnostic instruments. Bipolar illness may have subtle manifestations, but its recognition is essential to making proper management decisions. Mis-treatment can result in negative clinical outcomes, including prolongation of the disease state through delay in diagnosis, induction of hypomania or mania, refractory illness, and, perhaps, rapid cycling or mixed-state conditions. A thorough search for the hypomanic syndrome is mandatory in every depressed patient. An assessment of temperament and personality profiles, family pedigree, longitudinal course of the illness, and treatment response will also aid in identification of persons at risk.

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