

EVIDENCE-BASED CLINICAL MEDICINE

Is Your Depressed Patient Bipolar?

Neil S. Kaye, MD, DFAPA

Accurate diagnosis of mood disorders is critical for treatment to be effective. Distinguishing between major depression and bipolar disorders, especially the depressed phase of a bipolar disorder, is essential, because they differ substantially in their genetics, clinical course, outcomes, prognosis, and treatment. In current practice, bipolar disorders, especially bipolar II disorder, are underdiagnosed. Misdiagnosing bipolar disorders deprives patients of timely and potentially lifesaving treatment, particularly considering the development of newer and possibly more effective medications for both depressive features and the maintenance treatment (prevention of recurrence/relapse). This article focuses specifically on how to recognize the identifying features suggestive of a bipolar disorder in patients who present with depressive symptoms or who have previously been diagnosed with major depression or dysthymia. This task is not especially time-consuming, and the interested primary care or family physician can easily perform this assessment. Tools to assist the physician in daily practice with the evaluation and recognition of bipolar disorders and bipolar depression are presented and discussed. (J Am Board Fam Pract 2005;18:000–000.)

Studies have demonstrated that a large proportion of patients in primary care settings have both medical and psychiatric diagnoses and require dual treatment.¹ It is thus the responsibility of the primary care physician, in many instances, to correctly diagnose mental illnesses and to treat or make appropriate referrals. Much progress has been made over the past 2 decades in establishing the importance of depressive disorders in primary care settings and in improving their recognition and correct diagnosis. Because bipolar disorders tend to be a less-recognized illness, however, the possibility of bipolar disorder in a patient who presents with depressive features is rarely contemplated. Not a single mention of bipolar depression was made in a recent statement from the International Consensus Group on Depression and Anxiety.² This lack of attention has serious consequences, because morbidity and mortality, such as functional impairment and suicide, are substantially greater in bipolar dis-

orders than in major depression, and the psychiatric treatments of the 2 disorders are distinctly different.^{3–5} Whereas antidepressants are the treatment of choice for major depression, current guidelines recommend that antidepressants not be used in the absence of mood stabilizers in patients with a bipolar disorder,⁶ although more research is needed to clarify optimal treatment for patients with bipolar disorder who do not have type I disorder.⁷

Distinguishing between major depressive (unipolar) disorder and bipolar disorders, especially the depressive phase of bipolar disorders, is extremely important before instituting treatment for depression. “Unipolar” depression is characterized by a single mood pole, that of major depression, and fulfills specific defined criteria.⁸ Table 1 summarizes current DSM-IV-TR⁹ criteria for major depressive disorder. Bipolar disorders can be seen as having 3 distinct phases: the *depressed phase*, which mimics the clinical picture of major depression (lower pole), the *manic* or *hypomanic phase* (upper pole), and *euthymia*, or the asymptomatic phase. Tables 2 and 3 summarize diagnostic criteria for hypomania and mania. Manic and hypomanic episodes are characterized by grandiosity, inflated self-esteem, diminished need for sleep, increased goal-directed activity, and talkativeness. Mania and hypomania are distinguished by the fact that mania is of longer duration, causes more functional im-

T1

T2

T3

Submitted, revised, 14 April 2005.

From the Departments of Psychiatry and Family Medicine, Jefferson Medical College, Wilmington, Delaware.

Funding: This study was supported by an unrestricted grant from GlaxoSmithKline, Inc.

Conflict of interest: none declared.

Corresponding author: Neil S. Kaye, MD, DFAPA, Clinical Assistant Professor of Psychiatry and Family Medicine, Jefferson Medical College, 5301 Limestone Road, Suite 103, Wilmington, DE 19808 (e-mail: nskaye@aol.com).

AQ: G

Table 1. Diagnostic Criteria for Major Depressive Disorder

Major Depressive Episode

- ∞ Five or more of the following symptoms (present for at least 2 weeks):
 1. Depressed mood most of the day, nearly every day.
 2. Markedly diminished interest or pleasure in all, or almost all activities most of the day, nearly every day.
 3. Significant weight loss or weight gain.
 4. Insomnia or hypersomnia nearly every day.
 5. Psychomotor retardation or agitation nearly every day.
 6. Fatigue or loss of energy nearly every day.
 7. Feelings of worthlessness or excessive or inappropriate guilt nearly every day.
 8. Diminished ability to think or concentrate or indecisiveness nearly every day.
 9. Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt, or specific plan for committing suicide.
- ∞ Includes a change from previous functioning.
- ∞ At least one symptom is either depressed mood or loss of interest or pleasure.
- ∞ Note: Do not include symptoms due to a medical condition/mood incongruent delusions or hallucinations.
- ∞ Symptoms do not meet criteria for a Mixed Depressive Episode
- ∞ The symptoms cause clinically significant distress/impairment in social occupational, or other important areas of functioning.
- ∞ The symptoms are not due to a substance (drug abuse/medication) or general medical condition (eg, hypothyroidism).
- ∞ The symptoms are not better accounted for by bereavement.

Single Episode

- ∞ Presence of a single Major Depressive Episode.
- ∞ The Major Depressive Episode is not better accounted for by Schizoaffective Disorder and is not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified.
- ∞ There has never been a Manic Episode, a Mixed Episode, or a Hypomanic Episode.
Note: This exclusion does not apply if all of the manic-like, mixed-like, or hypomanic-like episodes are substance or treatment induced or are due to the direct physiological effects of a general medical condition.

Recurrent

- ∞ Presence of two or more Major Depressive Episodes.
Note: To be considered separate episodes, there must be an interval of at least 2 consecutive months in which criteria are not met for a Major Depressive Episode.
- ∞ The Major Depressive Episodes are not better accounted for by Schizoaffective Disorder and are not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified.
- ∞ There has never been a Manic Episode, a Mixed Episode, or a Hypomanic Episode.
Note: This exclusion does not apply if all of the manic-like, mixed-like, or hypomanic-like episodes are substance or treatment induced or are due to the direct physiological effects of a general medical condition.

Reprinted from American Psychiatric Association: Diagnostic and statistical manual of mental disorders, 4th ed, text rev. Washington DC: American Psychiatric Publishing, Inc; 2000. p. 375–6. Copyright © 2000 American Psychiatric Association. Used with permission.

pairment, and may be associated with psychotic features. Sometimes patients present with mixed episodes, in which patients experience both manic and depressive symptoms, with associated severe functional impairment. It is important to note that for a diagnosis of bipolar I disorder, only one lifetime manic or mixed episode is required.⁹ For a diagnosis of bipolar II disorder, the manual specifies that at least one hypomanic and one depressive episode occur in the absence of manic or mixed episodes.⁹

How Common Are Bipolar Disorders?

In the past, bipolar disorder was believed to have a prevalence of approximately 1.5%¹⁰; however, more

recent evidence suggests that actual prevalence rates approach 5.5% when the *spectrum* of bipolar illness is considered.^{11–15} This represents a continuum of mood states that includes the traditionally accepted bipolar I and bipolar II disorders, as well as mood swings that do not satisfy the DSM-IV defined criteria for bipolar I and II disorders but still result in significant functional impairment.^{12,15–18} This broader concept of bipolar disorders is currently evolving and remains an area of some debate among experts. Suffice it to say that bipolar disorders seem to be much more common than previously believed and are thus likely to be encountered with more frequency in the primary setting than previously thought.

Table 2. Diagnostic Criteria for Manic Episode

-
- ⌘ A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week (or any duration if hospitalization is necessary)
 - ⌘ During the period of mood disturbance, 3 or more of the following symptoms have persisted (4 if the mood is only irritable) and have been present to a significant degree:
 1. Inflated self-esteem or grandiosity
 2. Decreased need for sleep (eg, feels rested after only 3 hours of sleep)
 3. More talkative than usual or pressure to keep talking
 4. Flight of ideas or subjective experience that thoughts are racing
 5. Distractibility (ie, attention too easily drawn to unimportant or irrelevant external stimuli)
 6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
 7. Excessive involvement in pleasurable activities that have a high potential for painful consequences (eg, engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)
 - ⌘ The symptoms do not meet criteria for a Mixed Episode
 - ⌘ The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features
 - ⌘ The symptoms are not due to the direct physiological effects of a substance (eg, a drug of abuse, a medication, or other treatment) or a general medical condition (eg, hyperthyroidism)
- Note: Manic-like episodes that are clearly caused by somatic antidepressant treatment (eg, medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of Bipolar I Disorder
-

Reprinted from American Psychiatric Association: Diagnostic and statistical manual of mental disorders, 4th ed, text rev. Washington DC: American Psychiatric Publishing, Inc; 2000. p. 362. Copyright © 2000 American Psychiatric Association. Used with permission.

Misdiagnosing Bipolar Depression As Unipolar Depression

Awareness of a condition is a prerequisite for making the diagnosis. To paraphrase Voltaire, if you don't know about it you can't look for it; if you don't look for it, you can't find it. There is com-

elling evidence that both psychiatrists and primary care physicians miss the diagnosis of bipolar disorder, especially bipolar II disorder.¹⁹⁻²¹ Patients may also fail to mention the presence of manic or, more commonly, hypomanic symptoms in a past or current episode.²² This may be in part related to

Table 3. Diagnostic Criteria for Hypomanic Episode

-
- ⌘ A distinct period of persistently elevated, expansive, or irritable mood, lasting throughout at least 4 days, that is clearly different from the usual nondepressed mood.
 - ⌘ During the period of mood disturbance, 3 or more of the following symptoms have persisted (4 if the mood is only irritable) and have been present to a significant degree:
 1. Inflated self-esteem or grandiosity.
 2. Decreased need for sleep (eg, feels rested after only 3 hours of sleep).
 3. More talkative than usual or pressure to keep talking.
 4. Flight of ideas or subjective experience that thoughts are racing.
 5. Distractibility (ie, attention too easily drawn to unimportant or irrelevant external stimuli).
 6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation.
 7. Excessive involvement in pleasurable activities that have a high potential for painful consequences (eg, engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).
 - ⌘ The episode is associated with an unequivocal change in functioning that is uncharacteristic of the person when not symptomatic.
 - ⌘ The disturbance in mood and the change in functioning are observable by others.
 - ⌘ The episode is not severe enough to cause marked impairment in social or occupational functioning, or to necessitate hospitalization, and there are no psychotic features.
 - ⌘ The symptoms are not due to the direct physiological effects of a substance (eg, a drug of abuse, a medication, or other treatment) or a general medical condition (eg, hyperthyroidism).
- Note: Hypomanic-like episodes that are clearly caused by somatic antidepressant treatment (eg, medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of bipolar II disorder.
-

Reprinted from American Psychiatric Association: Diagnostic and statistical manual of mental disorders, 4th ed, text rev. Washington DC: American Psychiatric Publishing, Inc; 2000. p. 368. Copyright © 2000 American Psychiatric Association. Used with permission.

poor insight, which is predominant during manic episodes but may be present in all phases of the illness, even during remission.^{23–25} Despite low patient reporting rates and low physician pick-up rates, screening for bipolar disorders in patients presenting with depressive symptoms is seldom conducted, even in patients with a high risk of bipolar disorders.²⁶ As many as 40% of both inpatients and outpatients diagnosed with depression are subsequently found to have bipolar disorders.^{27,28} Most striking is that these were patients who had already experienced at least one manic or hypomanic episode before receiving the diagnosis of major depression. Similar findings have been demonstrated in other studies.^{29,30} In addition, an average of 8 years elapses from time of first presentation to correct diagnosis in patients with bipolar disorder.³¹

Therefore the problem of diagnosing bipolar disorders is threefold: current diagnostic classification failings contribute in part (see below), whereas failure of the physician to recognize previous hypomanic or manic symptoms and failure of patients to report them, also play a role.

Consequences of Misdiagnosis

Missing the diagnosis of a bipolar disorder could have serious and even occasionally fatal consequences for a person with the illness. Lifetime risk of suicide attempts among patients with bipolar disorders ranges from 25% to 50%,³² and estimates of completed suicide in persons with a bipolar disorder diagnosis are between 10% and 15%.⁷ Epidemiologic data also reveal that suicide attempts occur 30 times more frequently during depressive episodes than during manic or hypomanic states.⁴

Misdiagnosis and inappropriate treatment can also prolong suffering and contribute to worsening occupational, family, and social problems. The situation is particularly concerning because the use of antidepressants in bipolar depression, especially without the concomitant use of a mood stabilizer, may actually worsen the course of the disease. Antidepressants have been shown to contribute to rapid cycling,^{28,33} in which patients experience more mood swings than are normally seen, with at least 4 episodes of mania/hypomania and/or depression over a 1 year period. Rapid-cycling patients experience more episodes of illness, with progressively shorter periods of wellness and a

diminished response to medication.³⁴ At the present time, it is unclear whether the use of mood stabilizers in conjunction with an antidepressant protects against the development of rapid cycling.

Distinguishing between Unipolar and Bipolar Depression

As previously mentioned, a critical distinction between unipolar and bipolar depression is the presence of a history of manic or hypomanic symptoms in patients with bipolar disorders. Patients with bipolar II disorder are more frequently misdiagnosed than those with bipolar I disorder,²⁰ for the following reasons: (1) Often the patient feels remarkably well when hypomanic and is therefore unlikely to spontaneously report these episodes and may even deny them when directly questioned. (2) Patients with hypomania do not present with psychotic symptoms, and they are not hospitalized, so there may be no indication or records of a previous hypomanic episode.³ Several prominent researchers have argued that the usual duration of hypomanic symptoms is actually only 1 to 3 days^{12,15,35–38} and that current DSM-IV-TR diagnostic criteria (requirement for 4 days of hypomania) could incorrectly preclude the appropriate diagnosis in patients with hypomania of shorter duration.⁴ The clinical presentation of patients with mild hypomania may be irritability rather than the euphoria, or an exaggerated sense of well-being that is often associated with an elevated mood state, further challenging the physician.

On the other hand, as many as 35% to 60% of patients with bipolar disorders may experience an episode of major depression before experiencing a manic episode,²⁷ making the distinction between bipolar disorders and major depression (unipolar depression) substantially more difficult if not impossible. The presence of hypomanic or manic episode(s) is required to meet criteria for a diagnosis of bipolar disorders, and until that seminal episode occurs, it would be virtually impossible to diagnose anything other than major depression. However, as soon as the event occurs, the prior “misdiagnosis” needs to be updated to reflect the true bipolar disorder.

Making the Correct Diagnosis

In light of these challenges, what strategies can the busy primary care physician use to significantly

increase the recognition of bipolar disorders and bipolar depression, and particularly bipolar II depression (where frank mania has not been evidenced) in daily practice? Screening for hypomania and manic symptoms, identifying features that may be indicative of bipolar disorders, and careful patient interviews that include, when possible and appropriate, evidence from at least one other informant, are helpful to making the correct diagnosis.

Screening for Manic and Hypomanic Symptoms

Ruling out bipolar disorders should be a routine part of the workup for all patients who present acutely with depressive symptoms or who report a history of depression. As is the case with other medical disorders, the use of a brief, standardized screening instrument can be quite helpful. The Mood Disorder Questionnaire (MDQ) is a good tool for this purpose.³⁹ The MDQ is a 1-page questionnaire with 13 yes/no items and 2 additional questions regarding function and timing of symptoms (Appendix A). In a validation study of the MDQ, a score of 7 or above yielded a sensitivity of 73% and a specificity of 90%.³⁹ Any patient can easily complete this survey in less than 5 minutes, enabling its integration into a routine office visit, when the patient can fill it out before seeing the physician. It is important to note there is recent evidence to suggest that the MDQ tends to underdiagnose bipolar II disorder because of its requirement for moderate to severe impairment of func-

tioning, when improved functioning is frequently seen in those with hypomania.⁴⁰ The author has recommended removing the impairment criterion to appropriately diagnose bipolar II disorder.

AQ: A

Identifying Features of Bipolar Depression

A generation ago, it was widely believed that there were no differences between unipolar depression and bipolar depression.⁴¹ Since then, a number of clinical features have been recognized that may be used to distinguish between major depression (unipolar) and the depressed phase of a bipolar disorder (bipolar depression) or at least increase awareness of the possibility of a bipolar disorder diagnosis in a patient presenting with symptoms of depression (Table 4). These include younger age at onset (ie, <25 years),^{28,41-43} the presence of atypical symptoms,¹⁴ such as excessive sleepiness, and weight gain, as well as symptoms of psychomotor retardation,³⁰ the presence of psychotic features,^{22,44,45} and the presence of comorbid substance abuse.^{10,11} A family history of bipolar disorder can also point to the possibility of a bipolar diagnosis⁴⁶⁻⁴⁸ (see the Family History Screen by Weissman et al⁴⁹). Other features that can suggest the presence of bipolar illness in a depressed patient include multiple depressive recurrences (>3 episodes), brief duration of the depressive illness (<3 months), and past or current antidepressant-induced mania or hypomania,⁵⁰ as well as the presence of mixed

T4

Table 4. Features Indicative of Bipolar Disorders

	Bipolar	Unipolar
Substance abuse	Very high	Moderate
Family history	Almost uniform	Sometimes
Seasonality	Common	Occasional
First episode <25 years	Very common	Sometimes
Postpartum illness	Very common	Sometimes
Psychotic features <35 years	Highly predictive	Uncommon
Atypical features	Common	Occasional
Rapid on/off pattern	Typical	Unusual
Recurrent major depressive episodes (>3)	Common	Unusual
Antidepressant-induced mania or hypomania	Predictive	Uncommon
Brief major depressive episodes (avg <3 months)	Suggestive	Unusual (episode duration usually >3 months)
Wearing off of antidepressant efficacy	Suggestive	Uncommon
Mixed depression (presence of hypomanic features within the depressive episode)	Predictive	Rare

Data from refs. 7, 50, 54 (p. 114-9, 200-2), 51, 65, and 70.

depressive episodes, in which hypomanic symptoms are present during a depressive episode.⁵¹ A short-term, but not prolonged, response to antidepressants, where response to the antidepressant wears off over time is also suggestive of a bipolar disorder.⁵⁰

Bipolar illness is also characterized by a more pronounced seasonal pattern than is observed in major depression, with winter depressions being the most common.⁵² There is a greater likelihood of mood disturbance occurring during the postpartum period; as many as half of all women with bipolar spectrum disorder experience an episode of depression, mania, or mixed states after the birth of a child.⁵² In fact, for many women, the first presentation of a bipolar disorder is a postpartum episode.⁵³ Any woman without a prior psychiatric history who develops postpartum depression should be closely followed and monitored, as the risk for developing a bipolar disorder may be especially high.

Interviewing a Family Member or Other Informant

There are a number of reasons why it is advisable to attempt to interview the patient's spouse, parent, child, "significant other," or close friend. Patients may fail to recall manic or hypomanic symptoms or may have no insight into the impact their symptoms may have had on their functioning. On the other hand, many patients value their heightened activity and energy during hypomanic states and fail to report them as pathologic. Other patients may fear the stigma associated with bipolar disorders. Interviewing someone close to the patient can often provide historical clues to the correct diagnosis.²²

Treating the Patient with Bipolar Depression

Although correct identification of bipolar depression often lies in the hands of the primary care physician, referral or close consultation with a psychiatrist must be strongly considered in treating these patients. The psychopharmacology of the spectrum of bipolar disorders, and its many incarnations, is much more complicated and entails greater risk than that of major (unipolar) depression.⁵⁴ In addition, polypharmacy is the rule in these patients; only 20.6% of patients with bipolar disorders are managed with monotherapy.⁵⁵

A comprehensive discussion of pharmacotherapy for bipolar disorders is beyond the scope of this article; however, some key issues will be mentioned. Lithium has been the standard of treatment of bipolar disorders for many decades. In more recent years, the emergence of several anticonvulsants with mood stabilizing properties, among them divalproex, carbamazepine, and lamotrigine, as well increasing recognition of the utility of atypical antipsychotics, such as olanzapine, risperidone, quetiapine, and ziprasidone, has bolstered the physician's armamentarium for treating bipolar disorders.

The olanzapine-fluoxetine combination was recently approved for treatment of depressive episodes in bipolar disorders; this combination has been demonstrated to be efficacious based on an 8-week, randomized, controlled, double-blind trial in patients with bipolar depression.⁵⁶ Although there was no evidence of iatrogenic mania in this study,⁵⁶ the risk for developing mania associated with the use of fluoxetine will need to be adequately evaluated. Lithium, olanzapine, and lamotrigine are FDA-approved for maintenance therapy; lamotrigine's approval specifies use for maintenance therapy of bipolar I disorder.

The emergence of multiple newer agents for treating bipolar disorders has meant that medications can be selected for not only efficacy but also tolerability. Lithium has numerous side effects, a narrow therapeutic index, and a fatal overdose risk⁵⁷; however it is the only agent demonstrated to data to reduce risk of suicide in patients with bipolar disorders.⁵⁸⁻⁶⁰ Divalproex, which is used preferentially for manic rather than depressive states, is associated with weight gain, tremor, hepatotoxicity, and many drug-drug interactions.⁶¹ Carbamazepine, although never FDA-approved for the treatment of bipolar disorders, has been studied and shown to be efficacious, but it requires serum level monitoring and carries a risk of hyponatremia and a low risk of blood dyscrasia.⁶² Lamotrigine has demonstrated efficacy in bipolar depression⁶³ and in prevention of depressive recurrence in subjects with bipolar disorders.^{64,65} It must be carefully titrated and monitored to avoid the possibility of serious rash⁶⁶ but does not require blood monitoring and is associated with minimal weight gain, sexual side effects, sedation, or cognitive impairment. Olanzapine, quetiapine, risperidone, and some of the other atypical antipsychotics have been

AQ: B

AQ: C

AQ: D

associated with a dysmetabolic syndrome marked by weight gain,⁶⁷ increased risk of diabetes,⁶⁸ and elevated triglycerides, occasionally accompanied by pancreatitis. Therefore, monitoring of patients is required when these agents are to be used in the longer term, in conjunction with the American Diabetes Association/American Psychiatric Association Consensus Statement on Antipsychotic Medications and Obesity.⁶⁹

Antidepressant therapy in patients with bipolar disorders presents unique difficulties. Although treatment with antidepressant monotherapy is discouraged in current guidelines for bipolar disorder treatment,^{6,7} use of antidepressants may be necessary in some patients. The current APA guideline⁷ recommends use of bupropion and paroxetine as first-line antidepressant therapy; however, these are the only antidepressants that have been evaluated for use in bipolar disorders in randomized controlled trials to date that have demonstrated a relatively low risk of manic switch; therefore, conclusions cannot be drawn regarding their supremacy

over other antidepressants in treatment of bipolar disorders. Clinicians generally agree that other selective serotonin reuptake inhibitors, such as sertraline, are just as effective and safe and that monoamine oxidase inhibitors also are relatively unlikely to promote switching into mania.

Another reason to consider a psychiatric referral is that patients with bipolar disorders have a highly variable course of illness, with evolving, difficult-to-predict clinical features. Careful charting of mood symptoms (Appendix B) and ongoing psychiatric assessment are often required to clarify each patient's particular pattern of disease and provide optimal treatment. The extremely high incidence of comorbid substance abuse also complicates disease management and increases treatment noncompliance and negative outcomes.

Finally, the degree of psychosocial morbidity for people with bipolar disorders can be substantial.⁷ The divorce rate is 2 to 3 times higher than that of the general population,⁴⁶ and a majority of people so diagnosed experience some form of chronic oc-

Appendix A Mood Disorder Questionnaire Instructions: This questionnaire is an important part of providing you with the best health care possible. Your answers will help in understanding problems that you may have. Please answer each question as best you can.

	YES	NO
1. Has there ever been a period of time when you were not your usual self and...		
<input type="checkbox"/> you felt so good or so hyper that other people thought you were not your normal self or you were so hyper that you got into trouble?		
<input type="checkbox"/> you were so irritable that you shouted at people or started fights or arguments?		
<input type="checkbox"/> you felt much more self-confident than usual?		
<input type="checkbox"/> you got much less sleep than usual and found you didn't really miss it?		
<input type="checkbox"/> you were much more talkative or spoke much faster than usual?		
<input type="checkbox"/> thoughts raced through your head or you couldn't slow your mind down?		
<input type="checkbox"/> you were so easily distracted by things around you that you had trouble concentrating or staying on track?		
<input type="checkbox"/> you had much more energy than usual?		
<input type="checkbox"/> you were much more active or did many more things than usual?		
<input type="checkbox"/> you were much more social or outgoing than usual; for example, you telephoned friends in the middle of the night?		
<input type="checkbox"/> you were much more interested in sex than usual?		
<input type="checkbox"/> you did things that were unusual for you or that other people might have thought were excessive, foolish, or risky?		
<input type="checkbox"/> spending money got you or your family into trouble?		
2. If you checked YES to more than one of the above, have several of these ever happened during the same period of time?		
3. How much of a problem did any of these cause you—like being unable to work; having family, money, or legal troubles; getting into arguments or fights? <i>Please circle one response only.</i>		
No problem Minor problem Moderate problem Serious problem		
4. Have any of your blood relatives (ie, children, siblings, parents, grandparents, aunts, uncles) had manic depressive illness or bipolar disorder?		
5. Has a health professional ever told you that you have manic-depressive illness or bipolar disorder?		

Courtesy of The University of Texas Medical Branch. This instrument is designed for screening purposes only and is not to be used as a diagnostic tool.

cupational, social, or family difficulty,⁷ which may be alleviated to some extent by adjuvant psychosocial interventions.⁷ All these problems are more appropriately dealt with in a mental health setting.

Conclusion

Bipolar disorders are a very serious group of illness that are undoubtedly more commonly seen in primary care settings than was previously appreciated. They are associated with greater morbidity and mortality than major (unipolar) depression, and

treatments for unipolar depression and bipolar depression differ significantly. However, according to Bowden, “[e]very systematic study... finds [that]... a large proportion of patients with bipolar disorders receive a diagnosis of major depression.”²² This problem will persist until primary care physicians and even general psychiatrists develop a keen awareness of the possibility of the diagnosis of a bipolar disorder in patients presenting with symptoms of depression. This is particularly true for patients with bipolar II disorder, be-

Appendix B Mood Chart. *Instructions:* Patient should rate themselves each morning and evening (thus 2 columns for each date of the month). There is a normal range of mood and patient should use all three levels of 'normal.' The 3 levels of elevated and depressed mood should be viewed as mild, moderate, severe as defined by the patient. Name/ Month/Year

Date: AM/PM 1 1 2 2 3 3 4 4 5 5 6 6 7 7 8 8 9 9 10 10 11 11 12 12 13 13 14 14 15 15 16 16 17 17 18 18 19 19 20 20 21 21 22 22 23 23 24 24 25 25 26 26 27 27 28 28 29 29 30 30 31 31

Mood

- Severe elev.
- Moderate elev.
- Mild elevation
- Normal high
- Normal
- Normal low
- Mild dep.
- Moderate dep.
- Severe dep.

Circumstances

- Menses
- Thyroid function
- Alcohol
- Caffeine
- Hours slept

Medication

- Lithium dose
- Lithium level
- Depakote dose
- Depakote level
- Lamictal dose
- Lamictal level
- Tegretol dose
- Tegretol level

Other Meds

- Antidepressant
- Anxiolytic
- Sedative
- Antipsychotic

Special Events

- Notes:
 - Notes:
 - Notes:
-

cause their history does not include the more easily identifiable mania seen in bipolar I disorder. It is therefore imperative that physicians consider the differential diagnosis of bipolar disorders to be a routine component of the workup of any patient presenting with depressive symptoms or a history of depression. In addition, there is a need to address and revise existing diagnostic criteria for bipolar disorders to facilitate increased and appropriate recognition of the illness.

Although the diagnosis of bipolar disorder is frequently missed, there are several very useful strategies that can help physicians improve diagnostic accuracy: screening for manic symptoms, identifying features of the depression that are more typical of bipolar disorders, and interviewing a family member/significant other. Once the diagnosis is made, referral to a psychiatrist or working in close collaboration with a psychiatrist should result in the safest and most comprehensive treatment.

T5
T6

References

1. Stiebel V, Schwartz CE. Physicians at the medicine/psychiatric interface: what do internist/psychiatrists do? *Psychosomatics* 2001;42:377–81.
2. Ballenger JC, Davidson JR, Lecrubier Y, et al. Consensus statement on the primary care management of depression from the International Consensus Group on Depression and Anxiety. *J Clin Psychiatry* 1999;60 Suppl 7:54–61.
3. Angst J, Sellaro R. Historical perspectives and natural history of bipolar disorder. *Biol Psychiatry* 2000;48:445–57.
4. Compton MT, Nemeroff CB. The treatment of bipolar depression. *J Clin Psychiatry* 2000;61:57–67.
5. Thase ME, Sachs GS. Bipolar depression: pharmacotherapy and related therapeutic strategies. *Biol Psychiatry* 2000;48:558–72.
6. Sachs GS, Printz DJ, Kahn DA, Carpenter D, Docherty JP. The expert consensus guideline series: medication treatment of bipolar disorder 2000. *Postgrad Med* 2000;Spec No:1–104
7. American Psychiatric Association. Practice guideline for the treatment of patients with bipolar disorder (revision). *Am J Psychiatry* 2002;159:1–50.
8. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th ed. Washington DC: American Psychiatric Publishing, Inc; 1994.
9. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th ed, text rev. Washington DC: American Psychiatric Publishing, Inc; 2000.
10. Regier DA, Farmer ME, Rae DS, et al. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. *JAMA* 1990;264:2511–8.
11. Angst J. The emerging epidemiology of hypomania and bipolar II disorder. *J Affect Disord* 1998;50:143–51.
12. Angst J, Gamma A, Benazzi F, Ajdacic V, Eich D, Rossler W. Toward a re-definition of subthreshold bipolarity: epidemiology and proposed criteria for bipolar-II, minor bipolar disorders and hypomania. *J Affect Disord* 2003;73:133–46.
13. Akiskal HS, Bourgeois ML, Angst J, Post R, Moller H, Hirschfeld R. Re-evaluating the prevalence of and diagnostic composition within the broad clinical spectrum of bipolar disorders. *J Affect Disord* 2000;59 Suppl 1:S5–30.
14. Benazzi F. Depression with DSM-IV atypical features: a marker for bipolar II disorder. *Eur Arch Psychiatry Clin Neurosci* 2000;250:53–5.
15. Benazzi F. Frequency of bipolar spectrum in 111 private practice depression outpatients. *Eur Arch Psychiatry Clin Neurosci* 2003;253:203–8.
16. 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;73:123–31.
17. Akiskal HS, Pinto O. The evolving bipolar spectrum. Prototypes I, II, III, and IV. *Psychiatr Clin North Am* 1999;22:517–34, vii.
18. Goodwin FK, Jamison KR. Suicide. Manic-depressive illness. New York: Oxford University Press, Inc; 1990. p. 227–46.
19. Hirschfeld RM, Lewis L, Vornik LA. Perceptions and impact of bipolar disorder: how far have we really come? Results of the National Depressive and Manic-Depressive Association 2000 survey of individuals with bipolar disorder. *J Clin Psychiatry* 2003;64:161–74.
20. Manning JS, Haykal RF, Akiskal HS. The role of bipolarity in depression in the family practice setting. *Psychiatr Clin North Am* 1999;22:689–703, x.
21. Manning JS. Bipolar disorder in primary care. *J Fam Pract* 2003;Suppl:S6–9.
22. Bowden CL. Strategies to reduce misdiagnosis of bipolar depression. *Psychiatr Serv* 2001;52:51–5.
23. Pini S, Cassano GB, Dell’Osso L, Amador XF. Insight into illness in schizophrenia, schizoaffective disorder, and mood disorders with psychotic features. *Am J Psychiatry* 2001;158:122–5.
24. Dell’Osso L, Pini S, Cassano GB, Mastrocinque C, Seckinger RA, Sacttoni M, et al. Insight into illness in patients with mania, mixed mania, bipolar depression and major depression with psychotic features. *Bipolar Disord* 2002;4:315–22.
25. Yen CF, Chen CS, Yeh ML, Ker JH, Yang SJ, Yen JY. Correlates of insight among patients with bipolar I disorder in remission. *J Affect Disord* 2004;78:57–60.

26. Brickman AL, LoPiccolo CJ, Johnson SL. Screening for bipolar disorder. *Psychiatr Serv* 2002;53:349.
27. Ghaemi SN, Sachs GS, Chiou AM, Pandurangi AK, Goodwin K. Is bipolar disorder still underdiagnosed? Are antidepressants overutilized? *J Affect Disord* 1999;52:135–44.
28. Ghaemi SN, Boiman EE, Goodwin FK. Diagnosing bipolar disorder and the effect of antidepressants: a naturalistic study. *J Clin Psychiatry* 2000;61:804–8.
29. Hirschfeld RM. Bipolar spectrum disorder: improving its recognition and diagnosis. *J Clin Psychiatry* 2001;62 Suppl 14:5–9.
30. Benazzi F. Bipolar II disorder is common among depressed outpatients. *Psychiatry Clin Neurosci* 1999;53:607–9.
31. Lish JD, Dime-Meenan S, Whybrow PC, Price RA, Hirschfeld RM. The National Depressive and Manic-Depressive Association (DMDA) survey of bipolar members. *J Affect Disord* 1994;31:281–94.
32. Jamison KR. Suicide and bipolar disorder. *J Clin Psychiatry* 2000;61:47–51.
33. Wehr TA, Goodwin FK. Can antidepressants cause mania and worsen the course of affective illness? *Am J Psychiatry* 1987;144:1403–11.
34. Altshuler LL, Post RM, Leverich GS, Mikalaukas K, Rosoff A, Ackerman L. Antidepressant-induced mania and cycle acceleration: A controversy revisited. *Am J Psychiatry* 1995;152:1130–8.
35. Akiskal HS. The prevalent clinical spectrum of bipolar disorders: beyond DSM-IV. *J Clin Psychopharmacol* 1996;16:4S–14S.
36. Dunner DL, Tay LK. Diagnostic reliability of the history of hypomania in bipolar II patients and patients with major depression. *Compr Psychiatry* 1993;34:303–7.
37. Cassano GB, Dell’Osso L, Frank E, et al. The bipolar spectrum: a clinical reality in search of diagnostic criteria and an assessment methodology. *J Affect Disord* 1999;54:319–28.
38. Judd LL, Akiskal HS, Schettler PJ, et al. A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. *Arch Gen Psychiatry* 2003;60:261–9.
39. 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;157:1873–5.
40. Benazzi F. Improving the Mood Disorder Questionnaire to detect bipolar II disorder. *Can J Psychiatry* 2003;48:770–1.
41. Abrams R, Taylor MA. A comparison of unipolar and bipolar depressive illness. *Am J Psychiatry* 1980;137:1084–7.
42. Geller B, Craney JL, Bolhofner K, DelBello MP, Williams M, Zimmerman B. One-year recovery and relapse rates of children with a prepubertal and early adolescent bipolar disorder phenotype. *Am J Psychiatry* 2001;158:303–5.
43. Akiskal HS, Maser JD, Zeller PJ, et al. Switching from ‘unipolar’ to bipolar II. An 11-year prospective study of clinical and temperamental predictors in 559 patients. *Arch Gen Psychiatry* 1995;52:114–23.
44. Goldberg JF, Harrow M, Whiteside JE. Risk for bipolar illness in patients initially hospitalized for unipolar depression. *Am J Psychiatry* 2001;158:1265–70.
45. Goldberg AL, Elledge SJ, Harper JW. The cellular chamber of doom. *Sci Am* 2001;284:68–73.
46. Manning JS, Haykal RF, Connor PD, Akiskal HS. On the nature of depressive and anxious states in a family practice setting: the high prevalence of bipolar II and related disorders in a cohort followed longitudinally. *Compr Psychiatry* 1997;38:102–8.
47. Goodwin FK, Jamison KR. Medical treatment of acute bipolar depression. *Manic-depressive illness*. Oxford (UK): Oxford University Press, Inc.; 1990. p. 630–64.
48. Coryell W. Bipolar II disorder: the importance of hypomania. In: Goldberg JF and Harrow M, editors. *Bipolar disorders: clinical course and outcome*. Washington DC: American Psychiatric Publishing; 1999. p. 219–36.
49. Weissman MM, Wickramaratne P, Adams P, Wolk S, Verdelli H, Olfson M. Brief screening for family psychiatric history: the family history screen. *Arch Gen Psychiatry* 2000;57:675–82.
50. Ghaemi SN, Ko JY, Goodwin FK. The bipolar spectrum and the antidepressant view of the world. *J Psychiatr Pract* 2001;7:287.
51. Akiskal HS, Benazzi F. Family history validation of the bipolar nature of depressive mixed states. *J Affect Disord* 2003;73:113–22.
52. Whybrow PC. *A mood apart: depression, mania, and other afflictions of the self*. New York: HarperCollins; 1997.
53. Robling SA, Paykel ES, Dunn VJ, Abbott R, Katona C. Long-term outcome of severe puerperal psychiatric illness: a 23 year follow-up study. *Psychol Med* 2000;30:1263–71.
54. Potter WZ. Bipolar depression: specific treatments. *J Clin Psychiatry* 1998;59 Suppl 18:30–6.
55. Kupfer DJ, Frank E, Grochocinski VJ, Cluss PA, Houck PR, Stapf DA. Demographic and clinical characteristics of individuals in a bipolar disorder case registry. *J Clin Psychiatry* 2002;63:120–5.
56. Tohen M, Vieta E, Calabrese J, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. *Arch Gen Psychiatry* 2003;60:1079–88.
57. Physicians’ desk reference electronic library. Montvale (NJ): Medical Economics Company, Inc; 2002. Eskalith.
58. Tondo L, Baldessarini RJ, Floris G. Long-term clinical effectiveness of lithium maintenance treatment in types I and II bipolar disorders. *Br J Psychiatry Suppl* 2001;41:s184–90.
59. Goodwin FK, Fireman B, Simon GE, Hunkeler EM,

AQ: E

AQ: F

- Lee J, Revicki D. Suicide risk in bipolar disorder during treatment with lithium and divalproex. *JAMA* 2003;290:1467–73.
60. Kleindienst N, Greil W. Differential efficacy of lithium and carbamazepine in the prophylaxis of bipolar disorder: results of the MAP study. *Neuropsychobiology* 2000;42:2–10.
 61. Physicians' desk reference, 57th ed. Montvale (NJ): Thomson PDR; 2003. Depakote; p. 430–41.
 62. Physicians' desk reference electronic library. Montvale (NJ): Medical Economics Company, Inc; 2002. Tegretol.
 63. Calabrese JR, Bowden CL, Sachs GS, Ascher JA, Monaghan E, Rudd GD. A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. Lamictal 602 Study Group. *J Clin Psychiatry* 1999;60:79–88.
 64. Bowden CL, Calabrese JR, Sachs G, et al. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. *Arch Gen Psychiatry* 2003;60:392–400.
 65. Calabrese JR, Bowden CL, Sachs G, et al. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. *J Clin Psychiatry* 2003; 64:1013–24.
 66. Physicians' desk reference, 57th ed. Montvale (NJ): Thomson PDR; 2003. Lamictal; p. 1559–66.
 67. Allison DB, Casey DE. Antipsychotic-induced weight gain: a review of the literature. *J Clin Psychiatry* 2001;62 Suppl 7:22–31.
 68. Schwenkreis P, Assion HJ. Atypical antipsychotics and diabetes mellitus. *World J Biol Psychiatry* 2004; 5:73–82.
 69. American Diabetes Association; American Psychiatric Association; American Association of Clinical Endocrinologists; North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care* 2004;27:596–601.
 70. 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;47:125–34.

AUTHOR QUERIES

AUTHOR PLEASE ANSWER ALL QUERIES

1

A—Author: Which author has recommended removing the impairment criterion?

B—Author: Journal does not use 'gold standard,' even in quotation marks.

C—Author: The sentence here originally ('Numerous agents are approved for treating mania, among them a number of atypical antipsychotics, such as olanzapine, risperidone, quetiapine and ziprasidone.') seemed to be a repetition of the last sentence of the preceding paragraph, so it was deleted.

D—Author: Should 'to data' be 'to date' or 'by data'?

E—Author: In ref. 47, please clarify which is the book title and which is the chapter title.

F—Author: Please provide page numbers for refs. 57 and 62, if possible.

G—Author: Please specify which author is from each department.
