Tools to Improve Differential Diagnosis of Bipolar Disorder in Primary Care

J. Sloan Manning, MD

Among patients seen in a primary care setting for depressive and/or anxiety symptoms, 20% to 30% are estimated to have bipolar disorder. Although relatively common in primary care settings, bipolar disorder is still underrecognized, primarily due to misdiagnosis as unipolar depression. Patients often seek treatment when they are depressed but uncommonly present with mania or hypomania, the specific markers of bipolar spectrum disorders. An awareness of the prevalence, characteristics, and predictors of bipolar disorder can help the primary care physician to properly differentiate between bipolar depression and unipolar depression. Completing a differential diagnosis of bipolar disorder requires obtaining a comprehensive patient history that investigates symptom phenomenology and associated features, family history, longitudinal course of illness, and prior treatment response. In addition to the clinical interview, the Mood Disorder Questionnaire and the World Health Organization Composite International Diagnostic Interview 3.0 can be useful tools for evaluating patients for bipolar disorder. Screening patients at risk for bipolar disorder will help to avoid the use of unproductive or possibly even harmful treatments.
(Prim Care Companion J Clin Psychiatry 2010;12[suppl 1]:17–22)

The impact of bipolar disorder on patients and on the community is substantial. Patients with bipolar disorder report more difficulties with work performance, more disruptions in social life, and more difficulties with interpersonal relationships and are more likely to report being jailed or arrested than patients without bipolar disorder.[1,2] The impact continues even after syndromal recovery from a bipolar episode, with patients, particularly those experiencing episodes with psychotic features, often not having reached functional recovery 2 years later.[3] In addition, bipolar disorder is associated with increased rates of both psychiatric and medical comorbidities,[4,5] and with increased rates of mortality from diseases such as cardiovascular disease and diabetes and from causes such as suicide, homicide, or accidents.[6] Patients with bipolar disorder are frequent users of health care,[7] and bipolar disorder may be the most expensive psychiatric diagnosis to treat.[8]

In the past couple of decades, progress has been made in recognizing the high rate of mental disorders among primary care patients. A prevalence rate of nearly 30%, when including all psychiatric diagnoses, is now accepted, with mood and anxiety disorders accounting for the majority of these diagnoses.[9–11] In addition, although the community prevalence rate for bipolar disorder is about 4%,[12] a large study[13] (N = 1,157) in an urban general medicine clinic found nearly 10% of adult waiting room continuity patients screened positive for bipolar disorder using the Mood Disorder Questionnaire (MDQ).[14]

However, bipolar disorder among primary care patients has often been underrecognized, primarily due to misdiagnosis. For example, in the general primary care population mentioned above, more than two-thirds of those who screened positive for lifetime bipolar disorder had sought professional help for their symptoms, but the majority had been diagnosed with depression and/or anxiety.[13] Only 8% said they had ever received a diagnosis of bipolar disorder (or manic depression), and few of those who screened positive for bipolar disorder were taking mood stabilizers. An evaluation[15] conducted in a cohort of 108 consecutive anxious and/or depressed patients in a family practice setting identified 26% of the patients as having a bipolar spectrum disorder. Similarly, Hirschfeld and colleagues[16] screened a population of 649 family practice patients taking an antidepressant for depression and, using structured diagnostic interviews, estimated 27.9% of the patients as having bipolar disorder. Additionally, an investigation of consecutive patients with difficult to treat depression and anxiety referred to a primary mood disorder clinic found that 39% had bipolar disorder.[17]

Recognizing bipolar disorder can be difficult, but the examination of key elements of the patient's history via a clinical interview and the use of screening instruments can be crucial tools in the differential diagnosis of bipolar disorder. This article will address key topics to cover in the clinical interview, as well as screening instruments for bipolar disorder that have been validated for use in primary care.

From the Department of Family Medicine, University of North Carolina, Chapel Hill, and the Moses Cone Family Practice Residency and private practice, Greensboro, North Carolina.
This article is derived from the planning teleconference series "Improving the Recognition and Treatment of Bipolar Disorder in Primary Care," which was held in September 2009 and supported by an educational grant from AstraZeneca.
Dr Manning is a consultant for and is a member of the speakers/advisory boards for Eli Lilly and AstraZeneca.
Corresponding author: J. Sloan Manning, MD, 4446 Ashton Oaks Ct., High Point, NC 27265 (jsmanning@novanthealth.org).
doi:10.4088/PCC.9064su1c.03

For Clinical Use

- Bipolar disorder is a common but underrecognized diagnosis in primary health care settings.
- Completing a differential diagnosis for bipolar disorder requires obtaining a patient history that includes depressive symptoms and features, family psychiatric history, course of illness, and treatment response.
- Instruments such as the Mood Disorder Questionnaire (MDQ) and the World Health Organization Composite International Diagnostic Interview (CIDI) 3.0 can assist the physician in screening patients for bipolar disorder.

CLINICAL INTERVIEW FOR BIPOLAR DISORDER

The *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, Text Revision[18] (*DSM-IV-TR*) criteria for bipolar disorder require a current or past episode of mania or hypomania. However, the most common symptom of bipolar disorder is depression, with bipolar I patients experiencing depressive symptoms more than 3 times as frequently as manic or hypomanic symptoms[19] and bipolar II patients experiencing depressive symptoms approximately 39 times more often than hypomanic symptoms.[20] Therefore, physicians should evaluate patients presenting with depression for possible bipolar disorder, taking into consideration not only the patient's symptom phenomenology but also associated features, family history, course of illness, and history of treatment response (Table 1).[21]

Symptoms and Associated Features of Bipolar Disorder

Certain symptoms may be more common in bipolar depression than in unipolar depression. For instance, patients with bipolar depression more often experience atypical depressive features such as hypersomnia, hyperphagia, leaden paralysis, and rejection sensitivity. Mood lability, psychotic symptoms, psychomotor retardation, and pathological guilt are also more predictive of bipolar depression than unipolar depression.[22,23]

Hyperthymic and dysthymic temperaments can be another early presentation or predictor of bipolar disorder (Table 2).[24–26] Associated features of bipolar disorder, which can be helpful clues in the absence of a clear history of a manic or hypomanic state, include multiple (>2) divorces, tempestuous interpersonal relationships, romantic instability, use of multiple substances, an uneven employment history or frequent change in occupation, frequent change in city of residence, and legal and financial problems.[2,23,25]

Besides major depressive disorder (MDD), bipolar disorder may also be misdiagnosed as Axis II personality disorders, typically borderline or histrionic personality disorder.[27,28] For example, both bipolar II disorder and borderline personality disorder encompass irritability, impulsivity, and affective lability. However, bipolar II disorder seems to be associated more with attentional impulsiveness (eg, inability to focus on a task; racing thoughts), while borderline personality disorder is more related to nonplanning impulsiveness (eg, inability to think through consequences of actions).[29] Borderline personality disorder also appears to be associated with greater hostility than either bipolar disorder or MDD.

Family History

Family history is an informative component of the differential diagnosis of bipolar disorder. The relatives of patients with bipolar disorder are routinely more psychiatrically ill than those of patients with unipolar illness.[30,31] The family histories of patients with bipolar disorder may contain multiple individuals with substance use disorders, MDD, psychosis, multiple anxiety disorders, and attention-deficit/hyperactivity disorder. The clinical interview may elicit a family history of high levels of dysfunction and aberrant behaviors that involve contact with the legal system or other negative consequences of unstable mood, such as failed marriages or work-related problems. A history of either multiple first-degree and second-degree relatives with a major mood disorder or consecutive generations with an identifiable major mood disorder increases the likelihood that a patient presenting with depression has bipolar disorder, as does having a first-degree relative with an established diagnosis of bipolar disorder and/or a positive lithium response.[31–33]

Course of Illness

The longitudinal history of bipolar disorder can be confusing and sometimes misleading. Episodes of depression typically precede episodes of mania, perhaps by 5 to 10 years (Figure 1)[21]; this presentation can make a misdiagnosis of unipolar depression more likely. However, bipolar disorder is associated with an earlier age at onset than unipolar depression.[22,34,35] A retrospective study[35] of bipolar patients found that more than one-fourth of the participants experienced mood symptoms before the age of 13 years, and more than one-third experienced symptoms between ages 13 and 18 years.

In addition to an early age at onset, the course of bipolar disorder is characterized by more recurrence than MDD.[36,37] Some patients with bipolar disorder may experience a seasonal component[38] or rapid cycling of episodes.[36]

Treatment Response

Antidepressant nonresponse may be another indicator that the patient has bipolar disorder rather than MDD. Patients who have experienced no response to 3 or more antidepressant trials for depression should be evaluated for bipolar disorder, as antidepressants typically are not

© Copyright 2010 Physicians Postgraduate Press, Inc.

Table 1. Bipolar and Unipolar Depression: Distinguishing Factors[a]

Data Category/Diagnostic Variable	Bipolar	Unipolar
Phenomenology (morbid and temperamental)		
Spontaneous hypomania	+++	–
Atypical depression	+	+/–
Premorbid affective temperament, particularly hyperthymic or cyclothymic temperament	++	–
Mood lability	++	–
Increased mental/physical energy during depressions	++	–
Pedigree		
Family history of bipolar disorder or response to lithium	++	–
Loaded pedigree for the disorder	++	+/–
Longitudinal course		
Marital discord, frequent change in line of work or frequent relocation	++	+
High frequency of episodes	++	+
Early onset (age < 26 y) of mood disturbance	++	+
Treatment response		
Treatment-emergent hypomania/mania/mixed states[b]	+++	…
> 2 Antidepressant failures	++	+

[a]Reprinted with permission from Manning et al.[21]
[b]*DSM-IV* does not recognize treatment-emergent hypomania/mania as specific for bipolar illness. However, scientific evidence increasingly suggests otherwise.[38–40]
Symbols: + = approximated extent of presence in diagnostic category, – = not present.

Table 2. Temperamental Profiles[a]

Temperament	Profile
Dysthymic	Gloomy, pessimistic, hypercritical, passive, worrying, and conscientious with tendency to oversleep (> 10 hours/night)
Hyperthymic	Cheerful, overconscientious, impulsive, vigorous, meddlesome, uninhibited, and stimulus-seeking with tendency to undersleep (< 6 hours/night)
Cyclothymic	Cycling of moods from hypersomnic and introverted with psychomotor inertia to uninhibited and people-seeking with restless pursuit of activity
Irritable	Moody with angry, unprovoked outbursts; dysphoric restlessness; and intermittent insomnia

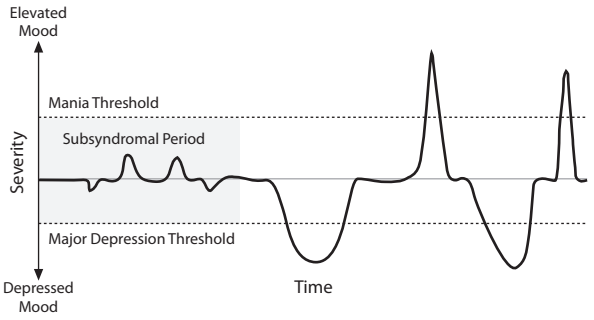
[a]Reprinted with permission from Cunningham et al.[26]

effective for bipolar depression. Conversely, patients may experience an uncharacteristically rapid response, usually an abrupt mood switch soon after starting the antidepressant, as antidepressants may trigger hypomania, which can be misinterpreted as a true response but which typically is erratic, lasting only days to a few weeks. Antidepressants can also mobilize full manic episodes or even mixed episodes, in which mania and depression exist at the same time. Suboptimal responses or antidepressant-induced hypomanic or mixed states can lead to the prescription of additional medications to treat symptoms such as agitation or anxiety, and to dose increases, augmentations, or switching of agents to treat the depression, but without a stable response.[39–41]

SCREENING INSTRUMENTS FOR BIPOLAR DISORDER

Once a patient's symptoms, associated features, family history, course of illness, and treatment response have been investigated, screening instruments may be helpful tools in further evaluating and differentiating mood symptoms. Two screening instruments for bipolar disorder that have been validated in the primary care setting are the MDQ and the Composite International Diagnostic Interview (CIDI).

Figure 1. Longitudinal Course of Bipolar I Illness[a]



[a]Reprinted with permission from Manning et al.[21]

Mood Disorder Questionnaire

The MDQ is a patient self-report instrument consisting of 3 questions (Table 3).[14] The first question is composed of 13 items describing mood or behaviors, which the patient endorses as either being present or not present during a previous period of abnormal mood. The next 2 questions establish the concurrence of any symptoms endorsed in the first question and the severity of functional impairment caused by the symptoms. If the patient endorses at least 7 of the 13 symptom items, confirms the concurrence of 2 or more symptoms during the same period of time, and rates his or her functional impairment due to the symptoms as moderate to severe, then the MDQ screen is considered positive.

A large validation study of the MDQ was conducted by Hirschfeld and colleagues[16] and included 649 patients in a family practice clinic who were receiving antidepressants for depression. Patients who screened positive on the MDQ then received the Structured Clinical Interview (SCID),[42] which is administered by a trained interviewer, for diagnostic confirmation. The MDQ was found to have a sensitivity of 58% and specificity of 93% for detecting bipolar disorder in primary care, which compared favorably to an earlier validation conducted in an outpatient psychiatric setting.[14]

Composite International Diagnostic Interview

Another bipolar disorder screening instrument of value to primary care physicians is the World Mental Health Survey Initiative version[43] of the World Health Organization CIDI 3.0 (Table 4).[44,45] The CIDI 3.0 is a brief structured clinical interview with 2 stem questions that are designed to identify distinct periods of elevated or expansive mood or persistently abnormal irritable mood (ie, the *DSM-IV-TR* Criterion A requirement for a manic or hypomanic episode). For those patients who answer a stem question affirmatively, a Criterion B screening question then checks for associated

© Copyright 2010 Physicians Postgraduate Press, Inc.

Table 3. Mood Disorder Questionnaire[a]

1. Has there ever been a period of time when you were not your usual self and …	YES	NO
… 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?	☐	☐
… you were so irritable that you shouted at people or started fights or arguments?	☐	☐
… you felt much more self-confident than usual?	☐	☐
… you got much less sleep than usual and found you didn't really miss it?	☐	☐
… you were much more talkative or spoke faster than usual?	☐	☐
… thoughts raced through your head or you couldn't slow your mind down?	☐	☐
… you were so easily distracted by things around you that you had trouble concentrating or staying on track?	☐	☐
… you had much more energy than usual?	☐	☐
… you were much more active or did many more things than usual?	☐	☐
… you were much more social or outgoing than usual, for example, you telephoned friends in the middle of the night?	☐	☐
… you were much more interested in sex than usual?	☐	☐
… you did things that were unusual for you or that other people might have thought were excessive, foolish, or risky?	☐	☐
… 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? *Please circle one response only.*

YES **NO**

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? *Please circle one response only.*

No Problem **Minor problem** **Moderate problem** **Serious Problem**

[a]Reprinted with permission from Hirschfeld et al.[14]

Table 4. Questions Used in the CIDI-Based Bipolar Disorder Screening Scale[a]

I. Stem questions

1. Some people have periods lasting several days or longer when they feel much more excited and full of energy than usual. Their minds go too fast. They talk a lot. They are very restless or unable to sit still and they sometimes do things that are unusual for them, such as driving too fast or spending too much money. Have you ever had a period like this lasting several days or longer?[b]
2. Have you ever had a period lasting several days or longer when most of the time you were so irritable or grouchy that you either started arguments, shouted at people, or hit people?

II. Criterion B screening question

1. People who have episodes like this often have changes in their thinking and behavior at the same time, like being more talkative, needing very little sleep, being very restless, going on buying sprees, and behaving in ways they would normally think are inappropriate. Did you ever have any of these changes during your episodes of being (excited and full of energy/very irritable or grouchy)?

III. Criterion B symptom questions

Think of an episode when you had the largest number of changes like these at the same time. During that episode, which of the following changes did you experience?

1. Were you so irritable that you either started arguments, shouted at people, or hit people?[c]
2. Did you become so restless or fidgety that you paced up and down or couldn't stand still?
3. Did you do anything else that wasn't usual for you — like talking about things you would normally keep private, or acting in ways that you'd usually find embarrassing?
4. Did you try to do things that were impossible to do, like taking on large amounts of work?
5. Did you constantly keep changing your plans or activities?
6. Did you find it hard to keep your mind on what you were doing?
7. Did your thoughts seem to jump from one thing to another or race through your head so fast you couldn't keep track of them?
8. Did you sleep far less than usual and still not get tired or sleepy?
9. Did you spend so much more money than usual that it caused you to have financial trouble?

[a]Reprinted with permission from Kessler et al.[45]
[b]If this question is endorsed, the irritability stem question is skipped and the respondent goes directly to the Criterion B screening question.
[c]This question is asked only if the euphoria stem question is endorsed.
Abbreviation: CIDI = Composite International Diagnostic Interview.

symptoms of mania. Patients who endorse this screening question are then asked to answer 15 yes-or-no Criterion B symptom questions; those who endorse 3 or more symptoms are asked additional questions to establish episode duration, severity of role impairment, and possible organic causes.

The CIDI 3.0 instrument has good discriminatory ability for the identification of bipolar disorder, depending on the number of manic symptom endorsements in the Criterion B symptom questions. A validation study[45] found high concordance rates with the SCID for diagnosing bipolar disorder, with the positive predictive value of the CIDI 3.0 being 41% to 88% depending on the bipolar spectrum disorder. The CIDI 3.0 was also validated across useful subsamples of the original study group (eg, high utilizers of primary care and low-income patients). This study also identified a brief version of the CIDI using the stem questions, the Criterion B screening question, and a subset of 9 questions of the 15 Criterion B symptom questions; this brief CIDI had a positive predictive value of 31% to 52%. Administering the CIDI has the potential added value of educating the primary care physician on an effective clinical interview using questions about bipolar disorder that are highly correlated with the proper diagnosis.

Practical Aspects of Screening

Screening instruments by themselves do not make a diagnosis, but the results are helpful when combined with the clinical interview, which elicits the key historical elements previously discussed. Using multiple screening tools might improve accuracy and correlation with the results of the clinical interview. For example, the MDQ and the CIDI 3.0 approach screening for bipolar disorder in different ways. The MDQ asks the patient to self-report previous symptoms of mania and the impairment from those symptoms in order to identify a manic episode, while the CIDI 3.0 frames

  © Copyright 2010 Physicians Postgraduate Press, Inc.

the screening in terms of first identifying an episode of either significantly elevated or persistently irritable mood and then endorsing associated symptoms of mania. Individual patients and clinicians may be more comfortable with (or more responsive to) one format over the other, so using both screening instruments might be useful in the same primary care practice. Clinician confidence in the diagnosis may be enhanced when 2 screening instruments are positive and correlate with both historical elements common for bipolar disorder and the clinical interview. Conflicting information may justify consultation or referral.

CONCLUSION

In practice, an initial diagnosis may not be accurate due to myriad reasons: patient histories might be misleading or inaccurate, patients may not remember symptoms, questions may not be framed correctly, or the patient may not be receptive to the questions. A good therapeutic alliance with the patient and multiple contacts with the patient over time will foster diagnostic precision and lead to more effective and appropriate treatment.

An awareness of the prevalence, characteristics, and predictors of bipolar disorder can help the primary care physician to recognize patients that need careful screening. In addition to a comprehensive patient history, the MDQ and the CIDI 3.0 can be useful instruments for evaluating patients for bipolar disorder. In cases of diagnostic dilemmas or severe patient symptoms, primary care physicians may choose to consult with, or refer patients to, a provider in the specialty mental health care sector.

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside US Food and Drug Administration–approved labeling has been presented in this activity.

REFERENCES

1. Calabrese JR, Hirschfeld RMA, Reed M, et al. Impact of bipolar disorder on a US community sample. *J Clin Psychiatry.* 2003;64(4):425–432.
2. Stang P, Frank C, Ulcickas Yood M, et al. Impact of bipolar disorder: results from a screening study. *Prim Care Companion J Clin Psychiatry.* 2007;9(1):42–47.
3. Tohen M, Hennen J, Zarate CM Jr, et al. Two-year syndromal and functional recovery in 219 cases of first-episode major affective disorder with psychotic features. *Am J Psychiatry.* 2000;157(2):220–228.
4. McElroy SL, Altshuler LL, Suppes T, et al. Axis I psychiatric comorbidity and its relationship to historical illness variables in 288 patients with bipolar disorder. *Am J Psychiatry.* 2001;158(3):420–426.
5. McIntyre RS, Konarski JZ, Yatham LN. Comorbidity in bipolar disorder: a framework for rational treatment selection. *Hum Psychopharmacol.* 2004;19(6):369–386.
6. Osby U, Brandt L, Correia N, et al. Excess mortality in bipolar and unipolar disorder in Sweden. *Arch Gen Psychiatry.* 2001;58(9):844–850.
7. Merikangas KR, Akiskal HS, Angst J, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication [published correction appears in Arch Gen Psychiatry. 2007;64(9)]. *Arch Gen Psychiatry.* 2007;64(5):543–552.
8. Peele PB, Xu Y, Kupfer DJ. Insurance expenditures on bipolar disorder: clinical and parity implications. *Am J Psychiatry.* 2003;160(7):1286–1290.
9. Regier DA, Narrow WE, Rae DS, et al. The de facto US mental and addictive disorders service system: Epidemiologic Catchment Area prospective 1-year prevalence rates of disorders and services. *Arch Gen Psychiatry.* 1993;50(2):85–94.
10. Mauksch LB, Tucker SM, Katon WJ, et al. Mental illness, functional impairment, and patient preferences for collaborative care in an uninsured, primary care population. *J Fam Pract.* 2001;50(1):41–47.
11. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. *JAMA.* 1999;282(18):1737–1744.
12. Hirschfeld RMA, Calabrese JR, Weissman MM, et al. Screening for bipolar disorder in the community. *J Clin Psychiatry.* 2003;64(1):53–59.
13. Das AK, Olfson M, Gameroff MJ, et al. Screening for bipolar disorder in a primary care practice. *JAMA.* 2005;293(8):956–963.
14. Hirschfeld RMA, Williams JBW, Spitzer RL, et al. Development and validation of a screening instrument for bipolar spectrum disorder: the Mood Disorder Questionnaire. *Am J Psychiatry.* 2000;157(11):1873–1875.
15. Manning JS, Haykal RF, Connor PD, et al. 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(2):102–108.
16. Hirschfeld RM, Cass AR, Holt DC, et al. Screening for bipolar disorder in patients treated for depression in a family medicine clinic. *J Am Board Fam Pract.* 2005;18(4):233–239.
17. Manning JS, Zylstra RG, Connor PD. Teaching family physicians about mood disorders: a procedure suite for behavioral medicine. *Prim Care Companion J Clin Psychiatry.* 1999;1(1):18–23.
18. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000.
19. Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry.* 2002;59(6):530–537.
20. 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(3):261–269.
21. Manning JS, Ahmed S, McGuire HC, et al. Mood disorders in family practice: beyond unipolarity to bipolarity. *Prim Care Companion J Clin Psychiatry.* 2002;4(4):142–150.
22. Mitchell PB, Goodwin GM, Johnson GF, et al. Diagnostic guidelines for bipolar depression: a probabilistic approach. *Bipolar Disord.* 2008; 10(1, pt 2):144–152.
23. Swann AC, Geller B, Post RM, et al. Practical clues to early recognition of bipolar disorder: a primary care approach. *Prim Care Companion J Clin Psychiatry.* 2005;7(1):15–21.
24. Akiskal HS. The temperamental borders of affective disorders. *Acta Psychiatr Scand Suppl.* 1994;379:32–37.
25. Akiskal HS. Searching for behavioral indicators of bipolar II in patients presenting with major depressive episodes: the "red sign," the "rule of three" and other biographic signs of temperamental extravagance, activation and hypomania. *J Affect Disord.* 2005;84(2-3):279–290.
26. Cunningham PD, Connor PD, Manning JS, et al. Evaluation of mood disorder patients in a primary care practice: measures of affective temperament, mental health risk factors, and functional health in a retrospective, descriptive study of 35 patients. *Prim Care Companion J Clin Psychiatry.* 2009;11(2):68–73.
27. Ruggero CJ, Zimmerman M, Chelminski I, et al. Borderline personality disorder and the misdiagnosis of bipolar disorder [published online ahead of print November 3, 2009]. *J Psychiatr Res.*
28. Berk M, Berk L, Moss K, et al. Diagnosing bipolar disorder: how can we do it better? *Med J Aust.* 2006;184(9):459–462.
29. Wilson ST, Stanley B, Oquendo MA, et al. Comparing impulsiveness, hostility, and depression in borderline personality disorder and bipolar II disorder. *J Clin Psychiatry.* 2007;68(10):1533–1539.
30. Gershon ES, Hamovit J, Guroff JJ, et al. A family study of schizoaffective, bipolar I, bipolar II, unipolar, and normal control probands. *Arch Gen Psychiatry.* 1982;39(10):1157–1167.
31. Wozniak J, Faraone SV, Mick E, et al. A controlled family study of children with DSM-IV bipolar-I disorder and psychiatric co-morbidity [published online ahead of print November 6, 2009]. *Psychol Med.*
32. Rende R, Birmaher B, Axelson D, et al. Childhood-onset bipolar disorder: evidence for increased familial loading of psychiatric illness. *J Am Acad Child Adolesc Psychiatry.* 2007;46(2):197–204.
33. Grof P, Duffy A, Alda M, et al. Lithium response across generations. *Acta Psychiatr Scand.* 2009;120(5):378–385.
34. Lish JD, Dime-Meenan S, Whybrow PC, et al. The National Depressive and Manic-Depressive Association (DMDA) survey of bipolar members. *J Affect Disord.* 1994;31(4):281–294.
35. Perlis RH, Miyahara S, Marangell LB, et al, for the STEP-BD Investigators. Long-term implications of early onset in bipolar disorder: data from the

© Copyright 2010 Physicians Postgraduate Press, Inc.

first 1000 participants in the systematic treatment enhancement program for bipolar disorder (STEP-BD). *Biol Psychiatry.* 2004;55(9):875–881.
36. Ghaemi SN, Bauer M, Cassidy F, et al, for the ISBD Diagnostic Guidelines Task Force. Diagnostic guidelines for bipolar disorder: a summary of the International Society for Bipolar Disorders Diagnostic Guidelines Task Force Report. *Bipolar Disord.* 2008;10(1, pt 2):117–128.
37. Goldberg JF, Harrow M, Whiteside JE. Risk for bipolar illness in patients initially hospitalized for unipolar depression. *Am J Psychiatry.* 2001;158(8):1265–1270.
38. Shin K, Schaffer A, Levitt AJ, et al. Seasonality in a community sample of bipolar, unipolar and control subjects. *J Affect Disord.* 2005;86(1):19–25.
39. Bunney WE Jr, Goodwin FK, Murphy DL, et al. The "switch process" in manic-depressive illness, pt II: relationship to catecholamines, REM sleep, and drugs. *Arch Gen Psychiatry.* 1972;27(3):304–309.
40. Altshuler LL, Post RM, Leverich GS, et al. Antidepressant-induced mania and cycle acceleration: a controversy revisited. *Am J Psychiatry.* 1995;152(8):1130–1138.
41. Benazzi F. Antidepressant-associated hypomania in outpatient depression: a 203-case study in private practice. *J Affect Disord.* 1997;46(1):73–77.
42. Spitzer RL, Williams JB, Gibbon M, et al. The Structured Clinical Interview for DSM-III-R (SCID), pt I: history, rationale, and description. *Arch Gen Psychiatry.* 1992;49(8):624–629.
43. Kessler RC, Ustün TB. The World Mental Health (WMH) Survey Initiative Version of the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI). *Int J Methods Psychiatr Res.* 2004;13(2):93–121.
44. World Health Organization. The World Health Organization (WHO) Composite International Diagnostic Interview (CIDI). http://www.hcp.med.harvard.edu/wmhcidi/index.php. Accessed December 10, 2009.
45. Kessler RC, Akiskal HS, Angst J, et al. Validity of the assessment of bipolar spectrum disorders in the WHO CIDI 3.0. *J Affect Disord.* 2006;96(3):259–269.

Go to PSYCHIATRIST.COM/pcc/bipolar to view
Table 1 and Figure 1 as enhanced graphics with audio.

© Copyright 2010 Physicians Postgraduate Press, Inc.