Undiagnosed Bipolar Disorder: New Syndromes and New Treatments

Ira D. Glick, M.D.

Recent studies have indicated that bipolar disorder is more common than previously believed. The socioeconomic and personal burdens of this illness are significant, and the lifetime risk of suicide attempts by patients with bipolar II disorder is high. It is not uncommon for patients with bipolar disorder, especially those presenting with depression, to be seen first in a primary care setting; therefore, primary care physicians need to be ready to diagnose and manage patients with these mental illnesses. The diagnosis of bipolar disorder or bipolar spectrum disorder is easily missed, or these illnesses may be misdiagnosed. A systematic and detailed initial history from the patient and a reliable family member is essential to making the correct diagnosis. The Mood Disorder Questionnaire, a validated screening instrument for bipolar disorder, may help primary care physicians make an appropriate diagnosis. Long-term management of patients with bipolar disorder should involve close liaison with a psychiatrist.

(Prim Care Companion J Clin Psychiatry 2004;6:27–33)

Received Nov. 5, 2003; accepted Jan. 21, 2004. From Stanford University Medical Center, Stanford, Calif.

Supported by an unrestricted educational grant from GlaxoSmithKline.

Dr. Glick has been a consultant for, received grant/research support and honoraria from, and served on the speakers or advisory boards of Pfizer, Eli Lilly, Bristol-Myers, Janssen, and AstraZeneca.

Corresponding author and reprints: Ira D. Glick, M.D., Stanford University Medical Center, Mail Code 5723, PBS #2200, 300 Pasteur Drive, Stanford, CA 94305-5723 (e-mail: ira.glick@stanford.edu).

PRIMARY CARE AND BIPOLAR DISORDER

While bipolar disorder is a complex psychiatric illness and is often more appropriately treated by a psychiatrist, it is not uncommon for patients with mental illness to be seen in a primary care setting, presenting either with problems related to the mental illness or with concerns totally unrelated to the psychiatric disorder. Either way, the primary care physician may be required to diagnose and manage patients with mental illnesses. A 1997 study[1] indicated that over 19.8% of patients who had scheduled primary care appointments fulfilled DSM-IV criteria for a psychiatric disorder; 8% of patients had any affective disorder, and approximately 1% had recognized bipolar disorder. It has also been demonstrated that about 50% of anxiety and depressive disorders are treated in a general medical setting.[2]

Recent evidence points to the fact that diagnoses of bipolar disorder, especially in patients with bipolar II disorder (who present more frequently with depressive episodes) or bipolar spectrum disorder, are frequently missed, both in psychiatric[3,4] and primary care settings.[5] The risk associated with missed diagnosis and misdiagnosis in these patients is great, and such patients, especially those presenting with depression, are frequently first seen and even treated in the primary care arena. It is, therefore, the responsibility of the primary care physician to recognize that bipolar disorder is more common than previously believed, that the burden associated with this disorder is significant, and that there is a need for improved diagnosis and recognition.

PREVALENCE OF BIPOLAR DISORDER

Historically, epidemiologic studies have indicated that prevalence rates for bipolar disorder are fairly low, with rates in the range of 1% to 2%.[6,7] More recent evidence has pointed to a much higher prevalence of bipolar disorder than was previously believed, with leaders in the field of bipolar disorder suggesting prevalence rates approximating 5% to 7%.[8–10] This higher prevalence estimation is probably due to a combination of increased recognition of the illness and acceptance of a broader definition of bipolar disorder, on the basis of 2 major advances over the last few years. A DSM-IV diagnosis of bipolar II disorder requires the presence of 1 episode of depression and 1 episode of hypomania. For a diagnosis of hypomania to be made, DSM-IV-TR (text revision)[11] now requires a duration of 4 days for hypomanic symptoms. Experts argue that episodes of shorter duration should be recognized in the criteria in order to prevent clinicians from ignoring shorter hypomanic episodes and thus misdiagnosing patients as having major depressive disorder.[10,11] The second advance has been the recognition of a "softer" spectrum of bipolar disorders,[8,12,13] or bipolar spectrum disorder. The concept of this disorder is evolving but is currently viewed as a longitudinal diagnosis consisting of mood swings that may include mania, hypomania, mixed states (which meet criteria for both a manic and a depressive episode), hyper-

thymic temperament (which describes a group of people who show cheerfulness and exuberance, meddlesomeness, lack of inhibitions, overconfidence, grandiosity, and high energy levels, in the absence of a formal thought disorder), major depressive disorder, and mixed depressive states (depression with 1 or 2 manic features).[14]

Recent epidemiologic data have confirmed suspicions among bipolar experts that bipolar disorder occurs more commonly than previously believed. The Mood Disorder Questionnaire (MDQ),[15] a validated screening instrument for bipolar disorders, was sent to a sample of approximately 130,000 people selected as representative of the U.S. adult population on the basis of demographic variables.[16] Prevalence of bipolar I and II disorders in the general U.S. population was 3.4%; the rate rose to 3.7% when adjusted for the nonresponse bias.[16] In addition, a recent secondary analysis of the U.S. National Epidemiologic Catchment Area (ECA) database[17] that reclassified respondents on the basis of the presence of at least 2 episodes of subthreshold symptoms of hypomania or mania of 1-week duration (features of bipolar spectrum disorder) found the prevalence rate for bipolar disorder to be 6.4%. Prevalence of subthreshold symptoms was 5.1%. The subthreshold group did not differ demographically from those with threshold manic or hypomanic symptoms. Compared with subjects from the no-mental-disorder comparison group, the subthreshold group had a 4 times higher suicide attempt rate, with a lifetime prevalence of 8%, significantly higher utilization of health care services, and a greater need for public assistance.

These findings would suggest that such patients should be treated if they are identified in the community setting; however, guidelines for diagnosis may need to be revisited before this becomes common practice. In this reanalysis of ECA data,[17] patients who had symptoms in the manic spectrum were more likely to be younger and have greater marital disruption than were patients in the other groups. The authors argue that although subjects with bipolar spectrum disorder do not fulfill existing criteria for a bipolar disorder diagnosis, they do fulfill criteria for "caseness" on the basis of their functional impairment. At present, no data exist that indicate whether and how many patients with such subthreshold symptoms progress to a diagnosis of bipolar I or II disorder.

BIPOLAR BURDEN

The socioeconomic and individual/family burdens related to bipolar disorder are significant. Studies to date have focused predominantly on bipolar disorder, rather than bipolar spectrum disorders, so it is conceivable that the true impact of the full spectrum of bipolar disorders remains unrecognized. In addition, there is no way of determining consequences related to unrecognized cases of bipolar disorder.

Socioeconomic Burden

The economic burden of bipolar disorder in the United States is substantial. Lifetime cost of bipolar disorder calculated in 1991 and 1998 was $45 billion[18] and $24 billion,[19] respectively; costs in the latter study were lower because indirect costs were not addressed. The 1998 study indicated that average direct medical care costs per patient ranged from $11,720 for patients with a single manic episode to $624,785 for patients with nonresponsive or chronic episodes.[19] Indirect costs in the 1991 study amounted to $38 billion and included lost productivity of wage earners, homemakers, and caregivers; institutionalization; and loss due to suicide.[18]

Personal Burden

The World Health Organization listed bipolar disorder as sixth on a list of 10 disorders that caused disability-adjusted life-years (DALYs) for males and females in developed countries.[20] DALYs are a measure of the burden of disease and reflect the total amount of healthy life lost from premature mortality or from disability.

Findings from 3 epidemiologic surveys have indicated that bipolar disorder is associated with substantial and long-lasting functional consequences.[21–23] Results from all 3 surveys have been remarkably similar. The most recent was a survey conducted among 600 bipolar support group participants of the National Depressive and Manic Depressive Association (DMDA).[21] Despite high levels of education (90% of respondents had attended some college), 57% were unemployed and greater than 50% reported household incomes of less than $15,000 per year. Sixty-five percent of respondents reported difficulty maintaining long-term intimate relationships; 34% were separated or divorced. The report[21] compared findings with an earlier, similar survey[24] and determined that very little had changed over the 8 years that had elapsed between surveys. Another recent survey[25] that evaluated the impact of bipolar disorder involved a sample of 3059 subjects taken from the larger sample of subjects in the Hirschfield et al. study.[16] Respondents who screened positive on the MDQ for bipolar disorder reported significantly higher levels of impairment in terms of work/school, social/leisure life, and family life on the Sheehan Disability Scale and the Social Adjustment Scale ($p < .0001$ for both scales). Significantly more ($p < .0001$) MDQ-positive respondents than MDQ-negative respondents reported being fired or laid off (54% vs. 29%) or being jailed, arrested, or convicted of a crime aside from drunk driving (26% vs. 5%).[25]

Suicide

A review of 15 studies determined that 25% to 50% of people with bipolar disorder attempt suicide at least once; completed suicide was more common among women.[26] Although bipolar II disorder has traditionally been viewed as resulting in less functional impairment than bipolar I

disorder, the lifetime risk of suicide attempts was highest in patients with bipolar II disorder, lower in patients with bipolar I disorder, and lowest in patients with major depressive disorder in another review.[27] Bipolar II patients were also overrepresented among suicide completers.

Another survey of 258 patients admitted from 1996 to 1999 to the Stanley Foundation Bipolar Network—an international, multisite network investigating the characteristics and course of bipolar disorder—found that 28.3% of their bipolar I cohort and 25.5% of their bipolar II cohort had a history of 1 or more suicide attempts.[28]

Although these data are contradictory, the Stanley Foundation survey demonstrated that patients with bipolar II disorder had a risk of suicide almost equal to their bipolar I counterparts, suggesting again that the longer-term risks associated with bipolar II disorder should not be underappreciated and that risk is high in both groups. Most suicides appear to occur in the depressed phase of the illness[29,30] and also commonly in association with comorbid substance abuse.[31,32]

SUBSTANCE ABUSE

The ECA study[6] reported that comorbid substance abuse occurred more frequently with bipolar disorder than with any other Axis I psychiatric disorder. Individuals with bipolar disorder abused or were dependent on drugs in 56% of cases and abused alcohol in 44% of cases. Post et al.[28] more recently conducted a survey indicating that 41.8% of individuals with bipolar I disorder and 25.5% of individuals with bipolar II disorder abused drugs or alcohol.

Bipolar disorder with comorbid substance abuse is associated with higher rates of refractoriness to lithium treatment[33,34] and higher risks of not only suicide attempts but also completed suicides.[31]

LONGER-TERM CONSEQUENCES OF BIPOLAR DISORDER

The Stanley Foundation Bipolar Network found that, in spite of treatment with a range of both novel and routinely used agents, two thirds of their group had clinically substantial depressive or manic symptoms over a year of follow-up.[28] Sixty-three percent of patients experienced 4 or more episodes per year; 31% had more than 8 episodes per year. Of the 33% of patients who were relatively well for most of the year, only 11% were virtually illness free.

Studies have indicated that most patients with bipolar disorder continue to show functional impairment, even patients who achieve euthymia.[35–38] Tohen et al.[35] assessed 219 patients hospitalized for an initial manic episode for functional recovery at regular intervals. Patients were assessed for syndromal recovery (i.e., no longer meeting DSM-IV criteria for mania) versus functional recovery (i.e., return to baseline vocational and residential status). At 6 months, 84% of patients achieved syndromal recovery, but only 30% achieved functional recovery. At 24 months, 98% of patients attained syndromal recovery, but only 38% attained functional recovery. Overall, only 37% of those patients showing syndromal recovery at 24 months achieved functional recovery. MacQueen et al.,[36] in an aggregate review of studies examining psychosocial outcome in bipolar disorder, found that 30% to 60% of individuals with bipolar disorder failed to regain full functioning occupationally and socially. There is also some evidence that patients with bipolar II disorder, compared with bipolar I disorder patients, experienced more illness disability in terms of health, recreation, finances, and subsyndromal depression.[39]

MISSED DIAGNOSIS AND MISDIAGNOSIS

There is convincing evidence that bipolar disorder is frequently either completely overlooked or misdiagnosed as major depressive disorder. The DMDA survey conducted in 2000[21] indicated that 69% of respondents with bipolar disorder were misdiagnosed. Those who were misdiagnosed received a mean of 3.5 alternative diagnoses and saw a mean of 4 physicians before they received an accurate diagnosis. Most respondents who reported being misdiagnosed believed that the greatest barrier to appropriate diagnosis was lack of understanding about bipolar disorder among health care professionals consulted. The most common incorrect diagnosis received was that of major depressive disorder (60% of cases); other diagnoses included anxiety disorder (26%), schizophrenia (18%), and borderline or antisocial personality disorder (17%). Forty-eight percent of respondents reported a lapse of several months to 5 years between seeking the first treatment and receiving an appropriate diagnosis; more than a third of patients reported a lapse of 10 years or more. The extensive gap between treatment-seeking and appropriate diagnosis represents no significant change from the findings in the 1994 survey,[24] indicating that there has been little improvement in bipolar disorder recognition and diagnosis over the last decade. The 130,000-person population survey[16] indicated that of those patients who screened positive for bipolar disorder, only 20% had received a diagnosis from a physician; 31% said that they were diagnosed with major depressive disorder, and almost 50% said that they had been diagnosed with neither depression nor bipolar disorder.

Bipolar patients frequently present initially with depressive episodes.[40] As many as 35% to 60% of patients experience a major depressive episode before experiencing a manic episode.[3] In addition, patients tend to underreport their experience of hypomanic episodes,[14,41] hence the tendency for misdiagnosis as depression. Ghaemi et al.[3,4] determined in 2 separate studies that approximately

40% of those initially diagnosed with major depressive disorder were converted to a diagnosis of bipolar disorder; patients were misdiagnosed even after having experienced an episode of mania or hypomania.

CONSEQUENCES OF MISDIAGNOSIS

In most cases, antidepressants have been associated with risk for adverse outcomes in patients with bipolar disorder; a misdiagnosis of depression and treatment with antidepressants place approximately 30% to 40% of bipolar patients at risk for induction of manic episodes.[42–44] Patients with bipolar disorder who take antidepressants also have been thought to have an increased risk of promotion of rapid cycling,[4,42,45] which is defined in DSM-IV as at least 4 episodes of affective illness in 1 year, with individual episodes demarcated by 2 months of full or partial remission or a switch to the opposite pole, and which is associated with greater treatment resistance and poorer outcomes. A recent study, however, did not implicate tricyclic antidepressants or, by inference, selective serotonin reuptake inhibitors in the promotion of affective instability.[46] This naturalistic study followed 89 patients for 1 or more years, and resolution of rapid cycling was not associated with a reduction in tricyclic antidepressant use. More research is required in this area to clarify relative risks and benefits of antidepressant use. Current guidelines recommend prescribing antidepressants together with a mood stabilizer in patients with bipolar disorder.[47] Misdiagnosis and inappropriate treatment of patients with bipolar disorder also delay management with mood stabilizers[41] and may increase the risk of lithium resistance, which occurs as more episodes are experienced.[48] There is also some evidence that appropriate treatment of bipolar disorders can reduce suicide risk[49] and that earlier recognition and treatment of bipolar disorders in children and adolescents reduce subsequent risk of substance abuse.[50]

IMPROVING DIAGNOSTIC ACCURACY

It is only through increased awareness of bipolar disorder that clinicians will begin to consider the diagnosis of bipolar disorder. The key to diagnosis lies in taking a systematic and detailed initial history from the patient,[51] which may be particularly difficult given the time constraints of a busy office environment.[52] Because patients frequently present with depressive episodes and may not report hypomanic episodes, the clinician should ask specifically about previous and existing symptoms of mania and hypomania, especially the occurrence of hypomania after depressive episodes.[41] Patient information alone is of limited value, and taking collateral histories from close family or friends can aid substantially in making the diagnosis.[41] In addition, there are a number of presenting features that differentiate bipolar disorder from major depressive disorder, and these features should be specifically addressed during the assessment (Table 1). Presence of these distinguishing features may not aid in discriminating between bipolar I and bipolar II disorder but will raise suspicion of the possibility of a bipolar diagnosis and the need for referral to a psychiatrist for appropriate assessment. Unfortunately, to date little work has been done to aid with diagnosis of bipolar spectrum disorders, and more research is needed in this area.

Table 1. Features That Distinguish Bipolar Disorder From Unipolar Depression

Sudden onset of episodes[51,53]
Early age at onset of episodes[51,54,55]
Presence of psychosis[53,56,57]
Presence of psychomotor retardation[53,58,59]
Presence of atypical features such as hypersomnia[55,58]
Family history of bipolar disorder,[54,56,58,60] especially those with loaded pedigrees[58]

The MDQ,[15] a patient-rated screening tool much like the Beck Depression Inventory,[61] may also help to facilitate an appropriate diagnosis of bipolar disorder. The MDQ is not designed to aid in making the distinction among bipolar I, II, or spectrum disorders but merely to raise the possibility of a bipolar diagnosis. A screening score of 7 out of 13 or more items answered affirmatively on the MDQ yields good sensitivity (0.73) and better specificity (0.90).[15] Patients with scores above 7 should be thoroughly questioned regarding bipolar features and referred in cases where doubt exists.

MANAGING BIPOLAR DISORDER

Pharmacotherapeutic management of bipolar disorder is extremely complex, fraught with frequent nonresponse and resistance to treatment and side effects. Management requires trial-and-error use of medications, treatment of any comorbidities, polypharmacy, and regular blood level and organ system function monitoring. In addition, nonpharmacologic therapies such as cognitive-behavioral therapy,[62,63] psychoeducation,[64,65] and family therapy[65,66] may be helpful in these patients. For these reasons, bipolar disorder is best managed in a psychiatric setting, and referral of patients with bipolar disorder, as well as those suspected of having bipolar disorder, is the best course of action. Obviously, patients who present an acute risk for suicide should be acutely referred and managed, and the presence of factors that represent increased risk for impulsivity and suicide, such as comorbid alcohol and substance abuse, should also precipitate an acute referral.

Primary care physicians are often the first contacts for both the patient and the family and may be called upon to provide support to family members. An excellent resource for family and patient support and education is the Depression and Bipolar Support Alliance (formerly

the DMDA). The organization's Web site (http://www.dbsalliance.org) can be used to locate support groups near the patient's home.

In addition, longer-term care of the patient with bipolar disorder may fall within the remit of the primary care physician, as patients present with complaints both related and unrelated to their mental illness. A strong relationship of consultation-liaison between the primary care physician and the psychiatrist is recommended. Medical comorbidities are common, and conditions such as migraine[15,67,68] or obesity and its associated consequences,[69,70] such as type II diabetes,[71,72] may be frequently seen. Office visits should include assessment for emergence of these comorbidities, as well as the numerous side effects that can be encountered with the use of commonly used mood stabilizers, such as hypothyroidism[73] and more rarely renal failure[73] associated with lithium use and polycystic ovary syndrome[74] associated with valproate use in epileptic women.

Psychiatric comorbidities are also common in these patients, and office visits should include a brief screening history for emergence of evidence of disorders such as obsessive-compulsive disorder,[75] anxiety disorders, posttraumatic stress disorder, social phobia,[7] panic disorder,[76] and personality disorders.[77] As abuse of alcohol and other substances is so common in bipolar populations,[75,78] the primary care physician should always remain vigilant for these comorbidities in patients with bipolar disorder. Assessment of suicide risk, which is highly prevalent in both bipolar I and II populations, should be evaluated at each office visit.

Stable patients with bipolar disorder taking lithium or valproate may require regular serum level and renal, hepatic, hematologic, and thyroid function monitoring. The American Psychiatric Association's revised guidelines for management of bipolar disorder[47] recommend checking renal and thyroid function every 6 months in stable patients taking lithium and conducting tests of hematologic and hepatic function every 6 months in patients taking valproate. Therapeutic levels of lithium range from 0.5 to 1.2 mEq/L, and those of valproate range between 50 and 125 g/mL.[47] Lithium levels should be monitored every 2 months,[79] and valproate levels, every 3 months in stable patients.

As for any other medical condition, caution should always be taken in considering drug-drug interactions and synergistic, or additive, negative effects of drugs in patients with bipolar disorder.

Other management considerations for patients with bipolar disorder are beyond the scope of this article; however, for more information, the reader is referred to Glick et al.[80]

FUTURE DIRECTIONS

There is evidence that prevalence rates for bipolar disorder are much higher than previously reported and that bipolar disorder is commonly seen in the primary care setting. The socioeconomic, personal, and family burdens associated with bipolar disorder are substantial, but it is not clear from existing research whether the true impact of bipolar disorder is understood, given that it is so frequently unrecognized. Patients with bipolar spectrum and bipolar II disorders often present with depressive episodes that facilitate misdiagnosis of major depressive disorder and treatment with antidepressants, possibly worsening outcomes for these patients. While it is likely that patients with bipolar disorder are best managed in a psychiatry environment, it is frequently the responsibility of the primary care physician to identify the possibility of a diagnosis of bipolar disorder. Therefore, there is a need for the primary care clinician to be aware of the possible indicators of bipolar disorder in these patients and to make the appropriate management decisions, among them referral. The MDQ may be a useful screening tool to help in this endeavor. As long-term management of bipolar disorder is complex, a strong consultation-liaison relationship between the primary care physician and the psychiatrist is recommended.

Drug name: lithium (Eskalith, Lithobid, and others).

REFERENCES

1. Olfson M, Fireman B, Weissman MM, et al. Mental disorders and disability among patients in a primary care group practice. Am J Psychiatry 1997;154:1734–1740
2. 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;50:85–94
3. Ghaemi SN, Sachs GS, Chiou AM, et al. Is bipolar disorder still underdiagnosed? are antidepressants overutilized? J Affect Disord 1999;52:135–144
4. Ghaemi SN, Boiman EE, Goodwin FK. Diagnosing bipolar disorder and the effect of antidepressants: a naturalistic study [CME]. J Clin Psychiatry 2000;61:804–808
5. 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;38:102–108
6. 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;264:2511–2518
7. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. Arch Gen Psychiatry 1994;51:8–19
8. Akiskal HS. The prevalent clinical spectrum of bipolar disorders: beyond DSM-IV. J Clin Psychopharmacol 1996;16(2 suppl 1):4S–14S
9. Akiskal HS, Bourgeois ML, Angst J, et al. Re-evaluating the prevalence of and diagnostic composition within the broad clinical spectrum of bipolar disorders. J Affect Disord 2000;59(suppl 1):S5–S30
10. Angst J. The emerging epidemiology of hypomania and bipolar II disorder. J Affect Disord 1998;50:143–151
11. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders-Text Revision, Fourth Edition. Washington, DC: American Psychiatric Association; 2000
12. Dunner DL, Gershon ES, Goodwin FK. Heritable factors in the severity of affective illness. Sci Pro Amer Psychiatric Assn 1970;123:187–188
13. Klerman GL. The spectrum of mania. Compr Psychiatry 1981;22:11–20
14. Hirschfeld RM. Bipolar spectrum disorder: improving its recognition and

diagnosis. J Clin Psychiatry 2001;62(suppl 14):5–9
15. Hirschfeld RM, Williams JB, Spitzer RL, et al. Development and validation of a screening instrument for bipolar spectrum disorder: the Mood Disorder Questionnaire. Am J Psychiatry 2000;157:1873–1875
16. Hirschfeld RM, Calabrese JR, Weissman MM, et al. Screening for bipolar disorder in the community. J Clin Psychiatry 2003;64:53–59
17. Judd LL, Akiskal HS. The prevalence and disability of bipolar spectrum disorders in the US population: re-analysis of the ECA database taking into account subthreshold cases. J Affect Disord 2003;73:123–131
18. Wyatt RJ, Henter I. An economic evaluation of manic-depressive illness: 1991. Soc Psychiatry Psychiatr Epidemiol 1995;30:213–219
19. Begley CE, Annegers JF, Swann AC, et al. The lifetime cost of bipolar disorder in the US: an estimate for new cases in 1998. Pharmacoeconomics 2001;19:483–495
20. Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. Lancet 1997;349: 1436–1442
21. 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;64:161–174
22. Suppes T, Leverich GS, Keck PE, et al. The Stanley Foundation Bipolar Treatment Outcome Network, 2: demographics and illness characteristics of the first 261 patients. J Affect Disord 2001;67:45–59
23. Kupfer DJ, Frank E, Grochocinski VJ, et al. Demographic and clinical characteristics of individuals in a bipolar disorder case registry [CME]. J Clin Psychiatry 2002;63:120–125
24. 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;31:281–294
25. Calabrese JR, Hirschfeld RM, Reed M, et al. Impact of bipolar disorder on a US community sample. J Clin Psychiatry 2003;64:425–432
26. Tondo L, Baldessarini RJ, Hennen J. Lithium and suicide risk in bipolar disorder. Prim Psychiatry 1999;6:51–56
27. Rihmer Z, Pestality P. Bipolar II disorder and suicidal behavior. Psychiatr Clin North Am 1999;22:667–673
28. Post RM, Denicoff KD, Leverich GS, et al. Morbidity in 258 bipolar outpatients followed for 1 year with daily prospective ratings on the NIMH life chart method [CME]. J Clin Psychiatry 2003;64:680–690
29. Sachs GS, Yan LJ, Swann AC, et al. Integration of suicide prevention into outpatient management of bipolar disorder. J Clin Psychiatry 2001;62(suppl 25):3–11
30. Oquendo MA, Waternaux C, Brodsky B, et al. Suicidal behavior in bipolar mood disorder: clinical characteristics of attempters and nonattempters. J Affect Disord 2000;59:107–117
31. Goldberg JF, Singer TM, Garno JL. Suicidality and substance abuse in affective disorders. J Clin Psychiatry 2001;62(suppl 25):35–43
32. Leverich GS, Altshuler LL, Frye MA, et al. Factors associated with suicide attempts in 648 patients with bipolar disorder in the Stanley Foundation Bipolar Network [CME]. J Clin Psychiatry 2003;64:506–515
33. Frye MA, Altshuler LL. Selection of initial treatment for bipolar disorder, manic phase. Mod Probl Pharmacopsychiatry 1997;25:88–113
34. Goldberg JF, Garno JL, Leon AC, et al. A history of substance abuse complicates remission from acute mania in bipolar disorder. J Clin Psychiatry 1999;60:733–740
35. 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;157:220–228
36. MacQueen GM, Young LT, Robb JC, et al. Effect of number of episodes on wellbeing and functioning of patients with bipolar disorder. Acta Psychiatr Scand 2000;101:374–381
37. Cooke RG, Robb JC, Young LT, et al. Well-being and functioning in patients with bipolar disorder assessed using the MOS 20-Item short form (SF-20). J Affect Disord 1996;39:93–97
38. Gitlin MJ, Swendsen J, Heller TL, et al. Relapse and impairment in bipolar disorder. Am J Psychiatry 1995;152:1635–1640
39. Robb JC, Cooke RG, Devins GM, et al. Quality of life and lifestyle disruption in euthymic bipolar disorder. J Psychiatr Res 1997;31: 509–517
40. Perugi G, Micheli C, Akiskal HS, et al. Polarity of the first episode, clinical characteristics, and course of manic depressive illness: a systematic retrospective investigation of 320 bipolar I patients. Compr Psychiatry 2000;41:13–18
41. Bowden CL. Strategies to reduce misdiagnosis of bipolar depression. Psychiatr Serv 2001;52:51–55
42. Altshuler LL, Post RM, Leverich GS, et al. Antidepressant-induced mania and cycle acceleration: a controversy revisited. Am J Psychiatry 1995;152:1130–1138
43. Henry C, Sorbara F, Lacoste J, et al. Antidepressant-induced mania in bipolar patients: identification of risk factors. J Clin Psychiatry 2001; 62:249–255
44. Goldberg JF, Whiteside JE. The association between substance abuse and antidepressant-induced mania in bipolar disorder: a preliminary study [CME]. J Clin Psychiatry 2002;63:791–795
45. Wehr TA, Goodwin FK. Do antidepressants cause mania? Psychopharmacol Bull 1987;23:61–65
46. Coryell W, Solomon D, Turvey C, et al. The long-term course of rapid-cycling bipolar disorder. Arch Gen Psychiatry 2003;60:914–920
47. Hirschfeld RMA, Bowden CL, Perlis RH, et al. Practice Guideline for the Treatment of Patients With Bipolar Disorder [Revision]. Am J Psychiatry 2002;159:1–50
48. Swann AC, Bowden CL, Calabrese JR, et al. Differential effect of number of previous episodes of affective disorder on response to lithium or divalproex in acute mania. Am J Psychiatry 1999;156:1264–1266
49. Tondo L, Baldessarini RJ. Reduced suicide risk during lithium maintenance treatment. J Clin Psychiatry 2000;61(suppl 9):97–104
50. Geller B, Cooper TB, Sun K, et al. Double-blind and placebo-controlled study of lithium for adolescent bipolar disorders with secondary substance dependency. J Am Acad Child Adolesc Psychiatry 1998;37:171–178
51. Coryell W, Endicott J, Maser JD, et al. Long-term stability of polarity distinctions in the affective disorders. Am J Psychiatry 1995;152:385–390
52. Kassirer JP. Doctor discontent. N Engl J Med 1998;339:1543–1545
53. Strober M, Carlson G. Bipolar illness in adolescents with major depression: clinical, genetic, and psychopharmacologic predictors in a three- to four-year prospective follow-up investigation. Arch Gen Psychiatry 1982;39:549–555
54. Winokur G, Coryell W, Endicott J, et al. Further distinctions between manic-depressive illness (bipolar disorder) and primary depressive disorder (unipolar depression). Am J Psychiatry 1993;150:1176–1181
55. Benazzi F. Sensitivity and specificity of clinical markers for the diagnosis of bipolar II disorder. Compr Psychiatry 2001;42:461–465
56. Goldberg JF, Harrow M, Whiteside JE. Risk for bipolar illness in patients initially hospitalized for unipolar depression. Am J Psychiatry 2001;158: 1265–1270
57. Mitchell PB, Wilhelm K, Parker G, et al. The clinical features of bipolar depression: a comparison with matched major depressive disorder patients. J Clin Psychiatry 2001;62:212–216
58. Akiskal HS, Walker P, Puzantian VR, et al. Bipolar outcome in the course of depressive illness: phenomenologic, familial, and pharmacologic predictors. J Affect Disord 1983;5:115–128
59. Kuhs H, Reschke D. Psychomotor activity in unipolar and bipolar depressive patients. Psychopathology 1992;25:109–116
60. Simpson SG, Folstein SE, Meyers DA, et al. Bipolar II: the most common bipolar phenotype? Am J Psychiatry 1993;150:901–903
61. Beck AT, Ward CH, Mendelson M, et al. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561–571
62. Lam DH, Watkins ER, Hayward P, et al. A randomized controlled study of cognitive therapy for relapse prevention for bipolar affective disorder: outcome of the first year. Arch Gen Psychiatry 2003;60:145–152
63. Otto MW, Reilly-Harrington NA. Cognitive-behavioural therapy for the management of bipolar disorder. In: Hofmann SG, Tompson MC, eds. Treating Chronic and Severe Mental Disorders: A Handbook of Empirically Supported Interventions. 1st ed. New York, NY: The Guilford Press; 2002
64. Colom F, Vieta E, Martinez-Aran A, et al. A randomized trial on the efficacy of group psychoeducation in the prophylaxis of recurrences in bipolar patients whose disease is in remission. Arch Gen Psychiatry 2003;60:402–407
65. Miklowitz DJ, Simoneau TL, George EL, et al. Family-focused treatment of bipolar disorder: 1-year effects of a psychoeducational program in conjunction with pharmacotherapy. Biol Psychiatry 2000;48:582–592
66. Miklowitz DJ, Goldstein MJ, Nuechterlein KH, et al. Family factors and the course of bipolar affective disorder. Arch Gen Psychiatry 1988; 45:225–231
67. Fasmer OB. The prevalence of migraine in patients with bipolar and

unipolar affective disorders. Cephalalgia 2001;21:894–899
68. Fasmer OB, Oedegaard KJ. Clinical characteristics of patients with major affective disorders and comorbid migraine. World J Biol Psychiatry 2001;2:149–155
69. McElroy SL, Frye MA, Suppes T, et al. Correlates of overweight and obesity in 644 patients with bipolar disorder. J Clin Psychiatry 2002;63:207–213
70. Fagiolini A, Frank E, Houck PR, et al. Prevalence of obesity and weight change during treatment in patients with bipolar I disorder. J Clin Psychiatry 2002;63:528–533
71. Cassidy F, Ahearn E, Carroll BJ. Elevated frequency of diabetes mellitus in hospitalized manic-depressive patients. Am J Psychiatry 1999;156: 1417–1420
72. Lilliker SL. Prevalence of diabetes in a manic-depressive population. Compr Psychiatry 1980;21:270–275
73. Markowitz GS, Radhakrishnan J, Kambham N, et al. Lithium nephrotoxicity: a progressive combined glomerular and tubulointerstitial nephropathy. J Am Soc Nephrol 2000;11:1439–1448
74. Isojarvi JI, Laatikainen TJ, Pakarinen AJ, et al. Polycystic ovaries and hyperandrogenism in women taking valproate for epilepsy. N Engl J Med 1993;329:1383–1388
75. US Dept Health and Human Services and National Institute of Mental Health. Epidemiologic Catchment Area (ECA) Survey of Mental Disorders, Wave I (household), 1980–1985: [United States]. Ann Arbor, Mich: Inter-university Consortium for Political and Social Research; 1991
76. Chen YW, Dilsaver SC. Comorbidity of panic disorder in bipolar illness: evidence from the Epidemiologic Catchment Area Survey. Am J Psychiatry 1995;152:280–282
77. Vieta E, Colom F, Corbella B, et al. Clinical correlates of psychiatric comorbidity in bipolar I patients. Bipolar Disord 2001;3:253–258
78. Cassidy F, Ahearn EP, Carroll BJ. Substance abuse in bipolar disorder. Bipolar Disord 2001;3:181–188
79. Eskalith (lithium carbonate). Physicians' Desk Reference. Montvale, NJ: Medical Economics, Inc; 2003:1515–1516
80. Glick ID, Suppes T, DeBattista C, et al. Psychopharmacologic treatment strategies for depression, bipolar disorder, and schizophrenia. Ann Intern Med 2001;134:47–60