CLINICAL PRACTICE

Bipolar Disorder — A Focus on Depression

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A 26-year-old businesswoman seeks evaluation for a pattern of "hibernating away" each winter; this pattern began when she was in high school. Her current symptoms include excessive sleeping, a 20-lb (9-kg) weight gain related to an increased intake of sweets and excessive alcohol use, anhedonia, lack of motivation, negative ruminations, and decreased productivity at work. She reports a history of several-week periods in college when she had less need for sleep, with associated increases in mood, energy, and libido. During the last episode, she exceeded her credit-card limit and was evaluated at an emergency department for alcohol intoxication. How should she be evaluated and treated?

THE CLINICAL PROBLEM

Bipolar disorder, a medical illness with substantial morbidity and mortality, is characterized by episodic recurrent mania or hypomania and major depression.[1] The hallmark of bipolar disorder is at least one episode of mania (bipolar I disorder) or hypomania (bipolar II disorder) (Table 1).[2] The greater severity of the elevated mood and the associated functional disability distinguish bipolar I mania (which is characterized by psychosis, the need for urgent care or hospitalization, or marked impairment) from bipolar II hypomania. In contrast to patients with mania, patients with hypomania infrequently seek evaluation unless a bipolar diagnosis is already established and there is concern regarding progression of the illness (i.e., becoming manic). Whereas the older term "manic-depressive illness" implied a depressive episode after each episode of mania, many patients present with one or more episodes of major depression before the first manic or hypomanic episode that defines bipolar disorder. The diagnostic criteria for an episode of major depression in bipolar disorder are the same as the criteria for unipolar major depressive disorder (Tables 1 and 2).

In a U.S. study,[3] the lifetime prevalence rate of bipolar disorder was 4.5% (1.0% for bipolar I disorder, 1.1% for bipolar II disorder, and 2.4% for manic and depressive symptoms that did not meet all the diagnostic criteria for bipolar I or bipolar II disorder). Bipolar disorder is associated with premature death and is among the leading causes of disability in the developed world in people 15 to 44 years of age.[4] The rate of completed suicide is approximately 5% among patients who have never been hospitalized, but it is as high as 25% early in the course of the illness.[5,6] The illness is frequently associated with other coexisting conditions, most commonly anxiety disorders and substance-use disorders.[7,8] These disorders are associated with an increased risk of suicidal ideation and of mood switches from depression to mania.[9,10]

Although the severity of mania is evident, most disability associated with bipolar disorder occurs in the depressive phase. In one study, there were significantly

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Table 1. Key Diagnostic Criteria Distinguishing Bipolar I Disorder from Bipolar II Disorder.*

Manic Episode (Bipolar I Disorder)	Hypomanic Episode (Bipolar II Disorder)
Distinct period during which there is an abnormally and persistently elevated, expansive, or irritable mood lasting at least 1 wk (or less if hospitalization is required)	Distinct period during which there is an abnormally and persistently elevated, expansive, or irritable mood lasting at least 4 days
Must be accompanied by at least three of the following symptoms (four if mood is only irritable): inflated self-esteem or grandiosity, decreased need for sleep, pressured speech, racing thoughts, distractibility, increased involvement in goal-directed activity or psychomotor agitation, excessive involvement in pleasurable activities with a high potential for painful consequences	Must be accompanied by at least three of the following symptoms (four if mood is only irritable): inflated self-esteem or grandiosity, decreased need for sleep, pressured speech, racing thoughts, distractibility, increased involvement in goal-directed activity or psychomotor agitation, excessive involvement in pleasurable activities with a high potential for painful consequences
Symptoms do not meet criteria for a mixed episode	Hypomanic episodes must be clearly different from the person's usual nondepressed mood, and there must be a clear change in functioning that is not characteristic of the person's usual functioning
Disturbance must be sufficiently severe to cause marked impairment in social or occupational functioning or to require hospitalization, or it is characterized by the presence of psychotic features	Changes in mood and functioning must be observable by others. In contrast to a manic episode, a hypomanic episode is not severe enough to cause marked impairment in social or occupational functioning or to require hospitalization, and there are no psychotic features
Symptoms not due to direct physiological effect of medication, general medical condition, or substance abuse	Symptoms not due to direct physiological effect of medication, general medical condition, or substance abuse

* Criteria are from the American Psychiatric Association.[2]

more work days lost per ill worker per year among patients with bipolar disorder than among those with unipolar major depression; the difference was driven primarily by recurrent depression, not mania.[11] Depressive episodes and low-level (i.e., subsyndromal) symptoms of depression typically last longer than manic episodes and low-level symptoms of mania. In the National Institute of Mental Health's Collaborative Depression Study involving patients with bipolar I disorder who were followed for more than 12 years, patients were symptomatic almost 50% of the time; depressive symptoms occurred about one third of the time, manic symptoms occurred about 10% of the time, and mixed symptoms occurred about 6% of the time.[12] Low-level symptoms of depression are also associated with functional disability[13] and subsequent depressive relapse.[14,15]

STRATEGIES AND EVIDENCE

DIAGNOSIS AND ASSESSMENT

The initial evaluation of a patient presenting with depressed mood should include screening for alcohol and drug use, assessment of suicidality, personal and family psychiatric history, and a physical examination and laboratory testing as indicated to rule out additional medical problems that may be contributing to symptoms. A meeting with significant others or family members may be helpful in obtaining additional information, particularly regarding the severity of symptoms. A family history of bipolar disorder, the onset of symptoms before 25 years of age, and more frequent episodes with a shorter duration (i.e., <6 months) increase the likelihood of a diagnosis of bipolar depression rather than unipolar depression.[1] Some, but not all, studies have also suggested that hypersomnia and hyperphagia are more common in bipolar depression, whereas insomnia (specifically early-morning awakening) and reduced appetite are more typical of unipolar depression.[1]

In conjunction with the clinical assessment, the Mood Disorder Questionnaire is a useful screening instrument for bipolar disorder in patients presenting with depression (see the Supplementary Appendix, available with the full text of this article at NEJM.org). This questionnaire includes 13 yes-or-no questions regarding symptoms that are typically associated with mania[16,17]; a "yes" answer to 7 or more questions about symptoms occurring concurrently and associated with at least moderate disability is considered a positive screening result. The Mood Disorder Questionnaire has been validated both in patients in outpatient psychiatric clinics and in the general population. However, recent studies have shown false positive rates between 15 and 30%, reflecting the overlap of symptoms of bipo-

lar disorder with those of other conditions such as attention-deficit disorder, eating disorders, substance-use disorder, post-traumatic stress disorder, and borderline personality disorder.[18,19]

Table 2. Diagnostic Criteria for Major Depression.*

Period of at least 2 wk during which five or more symptoms have been present (at least one of the symptoms is either depressed mood or loss of interest or pleasure in nearly all activities)
Changes in appetite or decrease or increase in weight, insomnia or hypersomnia, and psychomotor agitation or retardation; decreased energy; feelings of worthlessness or guilt; difficulty in thinking, concentrating, or making decisions; recurrent thoughts of death or suicidal ideation, plans, or attempts
Symptoms are either new or worse than before the depressive episode, and they persist for most of the day, nearly every day, for at least 2 consecutive wk
Episode accompanied by clinically significant distress or impairment in social, occupational, or other important areas of functioning
Symptoms are not due to bereavement or to direct physiological effect of medication, general medical condition, or substance abuse

* In major depression, the person's mood is described as depressed, sad, hopeless, discouraged, or "down in the dumps." Criteria are from the American Psychiatric Association.[2]

MANAGEMENT

FDA-Approved Treatments for Bipolar Depression

Although depression is more frequent than mania as a manifestation of bipolar disorder, medications for mania have been studied much more extensively. For acute mania, the Food and Drug Administration (FDA) has approved 10 treatments: one typical antipsychotic agent, lithium, two antiepileptic agents, and six atypical antipsychotic agents (Table 3). In contrast, there are only two FDA-approved treatments for bipolar depression — quetiapine and a combination of olanzapine and fluoxetine. Quetiapine and olanzapine are among several medications broadly defined as mood stabilizers, on the basis of their efficacy in treating acute mania or depression and in maintaining a clinical response without precipitating a switch to the alternate phase of the illness.

Four 8-week, placebo-controlled trials,[20-23] involving a total of 2593 subjects with bipolar I or bipolar II disorder, have demonstrated the efficacy of quetiapine monotherapy (at a dose of 300 mg or 600 mg) in treating bipolar depression. As compared with placebo, quetiapine resulted in a greater decrease from baseline to 8 weeks in the primary outcome measure (the score on the Montgomery and Åsberg Depression Rating Scale [MADRS], which ranges from 0 to 60, with higher scores indicating a greater severity of depressive symptoms), a higher rate of response (defined as a 50% reduction in symptoms), and a higher rate of symptom remission (MADRS score, 12 or lower). Outcomes associated with the 300-mg and 600-mg doses were similar. Two of the trials also included active comparison drugs: lithium[22] or the serotonin reuptake inhibitor paroxetine.[23] As compared with these other agents, quetiapine (at a dose of 300 mg or 600 mg daily) resulted in a greater decrease from baseline to 8 weeks in the MADRS score, higher rates of response and remission (except remission in the comparison of the 300-mg dose with paroxetine[23]), and a reduced rate of a switch to mania or hypomania (3.1% vs. 10.7% with paroxetine and 8.9% with placebo).

In another 8-week, randomized trial, involving 833 patients with bipolar I disorder, a combination of olanzapine (mean daily dose, 7.4 mg) and fluoxetine (mean daily dose, 39.3 mg) and olanzapine monotherapy (mean dose, 9.7 mg daily) were both superior to placebo in improving depression scores[24]; the overall decrease in the MADRS score was significantly greater with the olanzapine–fluoxetine combination than with olanzapine monotherapy. The rate of a switch to mania did not differ significantly between the drug combination (6.4%) and placebo (6.7%). Major concerns regarding both quetiapine and the olanzapine–fluoxetine combination are weight gain, with the associated risk of diabetes, and the risk of tardive dyskinesia. Although the risk of tardive dyskinesia cannot be estimated from these short-term trials, other data have indicated that the risk associated with atypical antipsychotic agents is significantly lower than the risk associated with typical (first-generation) antipsychotic agents (e.g., the risk associated with haloperidol is estimated to be 3 to 5% per year of exposure).[25] Data are lacking from longitudinal studies of tardive dyskinesia in patients with bipolar disorder who are receiving an atypical antipsychotic agent and have no history of exposure to typical antipsychotic agents.

The antidepressant effect reported for quetiapine and olanzapine–fluoxetine does not appear to be generalizable to other atypical antipsychotics. Using the same primary outcome measure, two double-blind, placebo-controlled trials involving a total of 749 patients with bipolar I disorder showed no significant antidepressant effect of aripiprazole, an agent approved for the treatment of mania and for maintenance

Table 3. Treatments for Bipolar Disorder.*

Drug Class and Agent	Dose	Research or Approval				Side Effects and Warnings
		Depression	Mania	Mixed Symptoms	Maintenance Therapy	
Atypical antipsychotic agent						Warnings for increased risk of death among elderly patients with dementia-related psychosis, neuroleptic malignant syndrome, tardive dyskinesia, hyperglycemia or diabetes, and seizures
Aripiprazole†	For acute mania or maintenance therapy, 15–30 mg/day	Controlled studies do not support use as monotherapy	FDA-approved	FDA-approved	FDA-approved	Extrapyramidal side effects, somnolence, and tremor
Asenapine†	For acute mania, 10 mg twice daily sublingually		FDA-approved	FDA-approved		Extrapyramidal side effects, weight gain, somnolence, and dizziness
Olanzapine†	For acute mania, 10–20 mg/day; for maintenance therapy, 5–20 mg/day	Controlled study supports use as monotherapy	FDA-approved	FDA-approved	FDA-approved	Extrapyramidal side effects, weight gain, dry mouth, dizziness, tremor, and gastrointestinal side effects; additional warnings for hyperlipidemia and hyperprolactinemia
Quetiapine and quetiapine, extended release†‡	For acute mania or maintenance therapy, 400–800 mg/day; for depression, 300–600 mg/day	FDA-approved	FDA-approved	FDA-approved	FDA-approved	Extrapyramidal side effects, weight gain, dry mouth, fatigue, and gastrointestinal side effects; additional warning for hyperlipidemia
Risperidone						
Oral†	For acute mania, 1–6 mg/day		FDA-approved	FDA-approved		Extrapyramidal side effects, somnolence, and gastrointestinal side effects; additional warning for hyperprolactinemia
Intramuscular§	25 mg every 2 wk				FDA-approved	
Ziprasidone‡	For acute mania or maintenance therapy, 80–120 mg/day	Controlled studies do not support use as adjunct or monotherapy	FDA-approved	FDA-approved	FDA-approved	Extrapyramidal side effects, somnolence, dizziness, asthenia, abnormal vision, and vomiting; additional warnings for QT prolongation and rash
Olanzapine–fluoxetine combination	6–12 mg and 25–50 mg once a day	FDA-approved				Fluoxetine associated with increased risk of suicidal thoughts and actions among some children, teenagers, and young adults

Antiepileptic drug						
Carbamazepine, extended release	For acute mania, 400–1600 mg in divided doses twice daily		FDA-approved	FDA-approved		Dizziness, somnolence, and coordination problems; warnings for serious rash, including Stevens–Johnson syndrome and toxic epidermal necrolysis (the risk of these two conditions is higher among patients with the HLA-B*1502 allele), agranulocytosis, suicidal ideation, teratogenicity, and aplastic anemia
Divalproex sodium, delayed or extended release	For acute mania, 25 mg/kg/day, with dose adjusted to obtain clinical response (85–125 μg/ml)	Meta-analysis supports use as monotherapy	FDA-approved	FDA-approved		Somnolence, gastrointestinal side effects, and dizziness; warnings for hepatotoxicity, pancreatitis, teratogenicity, thrombocytopenia, suicidal ideation, hyperammonemia, and hyperammonemic encephalopathy
Lamotrigine	Maintenance dose, 200–400 mg once a day	Meta-analysis supports use as monotherapy			FDA-approved	Headache, somnolence, nausea, fatigue, and insomnia; warnings for serious rash (including Stevens–Johnson syndrome and toxic epidermal necrolysis), hypersensitivity reaction, suicidal ideation, and aseptic meningitis
Lithium	For acute mania, gradually increase dose to obtain clinical response (0.8–1.2 mmol/liter)		FDA-approved		FDA-approved	Renal and thyroid dysfunction (baseline and periodic monitoring of renal and thyroid function recommended); lithium toxicity closely related to serum lithium levels

* FDA denotes Food and Drug Administration.
† This agent is indicated as both monotherapy and an adjunct to lithium or divalproex sodium for manic or mixed symptoms.
‡ This agent is indicated only as an adjunct to lithium or divalproex sodium for maintenance (i.e., prevention of manic, mixed, hypomanic, or depressive episodes).
§ This agent is indicated as both monotherapy and an adjunct to lithium or divalproex sodium for maintenance therapy (i.e., prevention of manic, mixed, hypomanic, or depressive episodes).

therapy (i.e., prevention of manic, mixed, or depressive episodes).[26] Similarly, in 6-week randomized trials, ziprasidone, another agent approved for mania and maintenance, was no more effective than placebo in reducing depressive symptoms when used either as monotherapy or adjunctive therapy.[27]

ANTIEPILEPTIC DRUGS

Lamotrigine, an FDA-approved drug for the maintenance treatment of bipolar I disorder,[28] has been suggested to have an additional antidepressant effect. A 7-week, randomized, double-blind, placebo-controlled trial of 200 mg of lamotrigine in 195 patients with bipolar I disorder showed significant decreases in scores on several depression rating scales.[29] Four subsequent placebo-controlled trials with varying inclusion criteria (patients with bipolar I disorder, bipolar II disorder, or both), trial duration (7 to 10 weeks), and dosing regimens (fixed dose, 50 mg vs. 200 mg; flexible dose, 100 to 400 mg) showed no significant benefit of lamotrigine. However, a recent meta-analysis[30] of all five trials (a total of 1072 patients) suggested a modest benefit of lamotrigine as assessed by a 50% or greater decrease in the MADRS score (relative risk, 1.22; 95% confidence interval [CI], 1.06 to 1.41; number needed to treat, 13) or the score on the Hamilton Rating Scale for Depression (relative risk, 1.27; 95% CI, 1.09 to 1.47; number needed to treat, 11). Remission rates were not significantly different as measured by the Hamilton Rating Scale, but they were slightly higher among patients who received lamotrigine, as measured by the MADRS; a prespecified subgroup analysis revealed a greater treatment effect in patients with severe depression.

Other data have also provided support for the use of lamotrigine in patients with bipolar depression. In an 8-week, randomized, placebo-controlled trial involving 124 outpatients with bipolar I or bipolar II disorder who were receiving lithium maintenance therapy, adjunctive therapy with 200 mg of lamotrigine resulted in greater improvement in the MADRS score and a higher response rate, as compared with placebo (51.6% vs. 31.7%).[31] A small, randomized, crossover trial involving 31 patients with refractory depression compared 6-week courses of lamotrigine, gabapentin, and placebo.[32] This trial showed that the percentage of patients whose depressive symptoms were much or very much improved was significantly greater with lamotrigine (52%) than with gabapentin (26%) or placebo (23%).

Divalproex sodium, which is approved for acute mania, has also been studied as monotherapy for bipolar depression. In a meta-analysis of four small, short-term, placebo-controlled trials involving 142 patients with bipolar I or II disorder,[33] divalproex monotherapy resulted in a significantly higher likelihood of clinical response and remission than placebo.

ANTIDEPRESSANT DRUGS

Despite a paucity of data to guide their use in patients with bipolar depression, antidepressant drugs are commonly prescribed. In a prescription-database study involving more than 7500 patients, 50% of all initial treatment prescriptions for bipolar disorder were for antidepressant monotherapy.[34] With the exception of fluoxetine, which is approved in combination with olanzapine for bipolar depression, all FDA-approved antidepressants are indicated only for unipolar depression; patients with a history of bipolar disorder were excluded from all registration trials.

Paroxetine is the selective serotonin-reuptake inhibitor (SSRI) that has been most rigorously studied in patients with bipolar depression,[23,35,36] and available efficacy data provide little support for its widespread use. As noted above, a randomized trial comparing paroxetine with quetiapine suggested that paroxetine was less effective in improving depression scores and was more likely to cause a switch to mania or hypomania.[23] In a randomized, placebo-controlled trial assessing adjunctive therapy with paroxetine (mean dose, 32.6 mg) or imipramine (mean dose, 166.7 mg) in patients with bipolar depression who were receiving lithium maintenance therapy, neither paroxetine nor imipramine was superior to placebo in reducing depressive symptoms at 10 weeks.[35] Finally, in a longer (26-week) trial in which 366 patients with bipolar I or bipolar II disorder who were receiving a mood stabilizer were randomly assigned to adjunctive antidepressant therapy (paroxetine or bupropion) or placebo,[36] there were no significant differences among groups in the rates of durable recovery, defined as 8 consecutive weeks of euthymia without a switch to mania or hypomania.

A meta-analysis of 15 randomized, double-blind trials comparing short-term antidepressant treatment (up to 4 months) with either placebo

or an active comparison drug in 2373 patients with bipolar I or II disorder likewise showed no major benefit of antidepressant therapy.[37] Six of these trials, involving 1469 patients, were placebo-controlled trials evaluating fluoxetine, paroxetine, imipramine, and bupropion; more than two thirds of the participants were receiving mood-stabilizing therapy. Although the definitions of outcomes varied among the studies, pooled analyses showed nonsignificant benefits of antidepressant therapy over placebo in the rates of response (relative risk, 1.18; 95% CI, 0.99 to 1.4; P=0.06) and remission (relative risk, 1.20; 95% CI, 0.98 to 1.47; P=0.09). Pooled analyses of data from more than 1000 of these patients suggested that antidepressant treatment did not increase the risk of a switch to mania or hypomania. In a smaller analysis comparing the antidepressants sertraline (an SSRI), bupropion, venlafaxine, and desipramine (a tricyclic antidepressant), the tricyclic antidepressant and venlafaxine were associated with higher rates of a switch to mania or hypomania than the other agents (desipramine, 43%; venlafaxine, 15%; sertraline, 7%; and bupropion, 5%).[37]

A meta-analysis of seven trials involved 350 patients with bipolar I or bipolar II disorder who were randomly assigned for at least 6 months to any type of antidepressant with or without a mood stabilizer or to placebo with or without a mood stabilizer. This study showed that antidepressant therapy reduced the risk of recurrent depression (relative risk, 0.73; 95% CI, 0.55 to 0.97) but increased the risk of a switch to a hypomanic or manic episode (relative risk, 1.72; 95% CI, 1.23 to 2.41).[38] Antidepressants may result in better outcomes in bipolar II disorder.[39] In a randomized trial of maintenance therapy in patients with bipolar II disorder, 81 patients with an initial response to open-label fluoxetine monotherapy were randomly assigned to continued treatment with fluoxetine, a change to treatment with lithium, or placebo for 50 weeks. The time to relapse or recurrence of depression, the primary outcome, was significantly longer with fluoxetine (250 days) than with lithium (156 days) or placebo (187 days). The risk of a switch to a hypomanic episode was no greater with fluoxetine (10.7%) or lithium (7.7%) than with placebo (18.5%).

PSYCHOTHERAPY

As compared with major depressive disorder, there has been little systematic evaluation of psychotherapy in patients with bipolar depression. The largest comparative trial of psychotherapy randomly assigned 293 outpatients with bipolar I or bipolar II disorder who were receiving medication to one of three forms of intensive psychotherapy (family-focused, interpersonal, or cognitive behavioral therapy) weekly or every other week up to 30 sessions, or to general psychoeducation for 3 sessions.[40] At 1 year, rates of recovery, defined as no more than one or two moderate symptoms of depression for at least 8 weeks, were significantly higher in the intensive-psychotherapy groups than in the group of patients who received general education (64% for the three psychotherapy groups combined vs. 52%).

AREAS OF UNCERTAINTY

More research is needed to determine which patients with bipolar depression might benefit from short-term or long-term antidepressant therapy without an undue risk of a switch to mania. Whereas more than 40% of subjects in one study retrospectively reported a switch to a manic or hypomanic episode within 12 weeks after starting an antidepressant at any time in their lives,[41] controlled clinical trials have suggested a much lower rate, prospectively confirmed (i.e., by rating-scale assessment).[23] However, patients with bipolar I disorder who are enrolled in trials of antidepressant monotherapy are carefully selected, and the risk of a switch to mania in these study populations may be substantially lower than the risk in clinical practice. In addition to tricyclic antidepressants[37] and possibly venlafaxine,[37,42] several clinical factors (e.g., whether the patient has bipolar I or bipolar II disorder and the lack of a mood stabilizer) have been associated with an increased risk of a switch to mania, and this risk should be taken into account in considering the risk–benefit ratio of antidepressants.[43]

A short-term, placebo-controlled trial showed the efficacy of modafinil, an agent approved to increase wakefulness in patients with certain sleep disorders, in bipolar depression.[44] Pramipexole, a partial dopamine-receptor subtype 2 and dopamine-receptor subtype 3 agonist approved for Parkinson's disease,[45,46] was also effective in improving symptoms of depression in two small, short-term trials (one involving patients with bipolar I disorder and the other involving patients with bipolar II disorder), although psychotic mania developed in one patient with bipolar I dis-

order after active treatment. More data are needed to determine the role of these agents in practice.

GUIDELINES

Guidelines for the treatment of bipolar depression are currently being revised by the American Psychiatric Association. The guidelines of the International Society for Bipolar Disorders recommend any of the following agents as first-line therapy for bipolar depression: quetiapine, lamotrigine, or lithium monotherapy; olanzapine with an SSRI (i.e., fluoxetine or another SSRI); and lithium or divalproex with an SSRI or bupropion.[47] These guidelines antedate the trials showing the superiority of quetiapine over lithium or paroxetine.

CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette has recurrent depression with current symptoms of hypersomnia and hyperphagia in the context of at least one previous manic episode (i.e., bipolar I disorder). She should be informed about the effect of her alcohol abuse on depression and should be encouraged to abstain from drinking and to consider specific treatment for alcohol dependency if hazardous drinking continues when her depression has been treated. Although both the fluoxetine–olanzapine combination and quetiapine are FDA-approved for bipolar depression, I would recommend the initiation of treatment with quetiapine (at a dose of 300 mg daily), given the amount of evidence that supports the use of this agent. Monitoring is warranted for somnolence, an elevation in the glucose level, weight gain, and tardive dyskinesia (although the risk of tardive dyskinesia is considered to be low). If quetiapine is poorly tolerated or if there is no change in depressive symptoms, lamotrigine (with a gradual increase to a dose of 200 mg) would be a reasonable second-line intervention. I would not recommend antidepressant monotherapy. If antidepressant cotherapy is used, careful monitoring is required for suicidal ideation and a switch to mania or hypomania during treatment.

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REFERENCES

1. Goodwin FK, Jamison KR. Manic-depressive illness: bipolar disorders and recurrent depression. 2nd ed. New York: Oxford University Press, 2007.
2. Diagnostic and statistical manual of mental disorders, 4th ed. rev.: DSM-IV-R. Washington, DC: American Psychiatric Association, 2000.
3. Merikangas KE, Akiskal HS, Angst J, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. Arch Gen Psychiatry 2007;64:543-52.
4. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. Lancet 1997;349:1498-504.
5. Tondo L, Isacsson G, Baldessarini R. Suicidal behaviour in bipolar disorder: risk and preventions. CNS Drugs 2003; 17:491-511.
6. Inskip HM, Harris EC, Barraclough B. Lifetime risk of suicide for affective disorder, alcoholism and schizophrenia. Br J Psychiatry 1998;172:35-7.
7. Frye MA, Altshuler LL, McElroy SL, et al. Gender differences in prevalence, risk, and clinical correlates of alcoholism comorbidity in bipolar disorder. Am J Psychiatry 2003;160:883-9.
8. Simon NM, Otto MW, Wisniewski SR, et al. Anxiety disorder comorbidity in bipolar disorder patients: data from the first 500 participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Am J Psychiatry 2004;161:2222-9.
9. Simon NM, Zalta AK, Otto MW, et al. The association of comorbid anxiety disorders with suicide attempts and suicidal ideation in outpatients with bipolar disorder. J Psychiatr Res 2007;41:255-64.
10. Ostacher MJ, Perlis RH, Nierenberg AA, et al. Impact of substance use disorders on recovery from episodes of depression in bipolar disorder patients: prospective data from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Am J Psychiatry 2010;167: 289-97.
11. Kessler RC, Akiskal HS, Ames M, et al. Prevalence and effects of mood disorders on work performance in a nationally representative sample of U.S. workers. Am J Psychiatry 2006;163:1561-8.
12. 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;59:530-7.
13. Altshuler LL, Gitlin MJ, Mintz J, Leight KL, Frye MA. Subsyndromal depression is associated with functional impairment in patients with bipolar disorder. J Clin Psychiatry 2002;63:807-11.
14. Perlis RH, Ostacher MJ, Patel JK, et al. Predictors of recurrence in bipolar disorder: primary outcomes from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Am J Psychiatry 2006;163:217-24.
15. Frye MA, Yatham LN, Calabrese JR, et al. Incidence and time course of subsyndromal symptoms in patients with bipolar I disorder: an evaluation of 2 placebo-controlled maintenance trials. J Clin Psychiatry 2006;67:1721-8.
16. 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;11:1873-5.
17. Hirschfeld RM, Holzer C, Calabrese JR, et al. Validity of the Mood Disorder Questionnaire: a general population study. Am J Psychiatry 2003;160:178-80.
18. Zimmerman M, Galione JN, Chelminski I, Young D, Dalrymple K. Psychiatric diagnoses in patients who screen positive on the Mood Disorder Questionnaire: implications for using the scale as a case-finding instrument for bipolar disorder. Psychiatry Res 2010 July 24 (Epub ahead of print).
19. Zimmerman M, Galione JN, Ruggero CJ, et al. Screening for bipolar disorder and finding borderline personality disorder. J Clin Psychiatry 2010;71:1212-7.
20. Calabrese JR, Keck PE Jr, Macfadden W, et al. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. Am J Psychiatry 2005;162:1351-60.
21. Thase ME, Macfadden W, Weisler RH, et al. Efficacy of quetiapine monotherapy in bipolar I and II depression: a double-blind, placebo-controlled study (the BOLDER II study). J Clin Psychopharmacol 2006;26:600-9. [Erratum, J Clin Psychopharmacol 2007;27:51.]
22. Young AH, McElroy SL, Bauer M, et al. A double-blind, placebo-controlled study of quetiapine and lithium monotherapy in adults in the acute phase of bipolar depression (EMBOLDEN I). J Clin Psychiatry 2010;71:150-62.
23. McElroy SL, Weisler RH, Chang W, et al. A double-blind, placebo-controlled study of quetiapine and paroxetine monotherapy in adults with bipolar depression (EMBOLDEN II). J Clin Psychiatry 2010; 71:163-74.
24. 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. [Erratum, Arch Gen Psychiatry 2004;61:176.]
25. Kane JM. Tardive dyskinesia circa 2006. Am J Psychiatry 2006;163:1316-8.
26. Thase ME, Jonas A, Khan A, et al. Aripiprazole monotherapy in nonpsychotic bipolar I depression: results of 2 randomized, placebo-controlled studies. J Clin Psychopharmacol 2008;28:13-20. [Erratum, J Clin Psychopharmacol 2009;29:38.]
27. ClinicalTrials.gov home page. (http://www.clinicaltrials.gov/.)
28. Goodwin GM, Bowden CL, Calabrese JR, et al. A pooled analysis of 2 placebo-controlled 18-month trials of lamotrigine and lithium maintenance in bipolar I disorder. J Clin Psychiatry 2004;65:432-41.
29. 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. J Clin Psychiatry 1999;60:79-88.
30. Geddes JR, Calabrese JR, Goodwin GM. Lamotrigine for treatment of bipolar depression: independent meta-analysis and meta-regression of individual patient data from five randomised trials. Br J Psychiatry 2009;194:4-9.
31. van der Loos ML, Mulder PG, Hartong EG, et al. Efficacy and safety of lamotrigine as add-on treatment to lithium in bipolar depression: a multicenter, double-blind, placebo-controlled trial. J Clin Psychiatry 2009;70:223-31.
32. Frye MA, Ketter TA, Kimbrell TA, et al. A placebo-controlled study of lamotrigine and gabapentin monotherapy in refractory mood disorders. J Clin Psychopharmacol 2000;20:607-14.
33. Bond DJ, Lam RW, Yatham LN. Divalproex sodium versus placebo in the treatment of acute bipolar depression: a systematic review and meta-analysis. J Affect Disord 2010;124:228-34.
34. Baldessarini RJ, Leahy L, Arcona S, Gause D, Zhang W, Hennen J. Patterns of psychotropic drug prescription for U.S. patients with diagnoses of bipolar disorders. Psychiatr Serv 2007;58:85-91.
35. Nemeroff CB, Evans DL, Gyulai L, et al. Double-blind, placebo-controlled comparison of imipramine and paroxetine in the treatment of bipolar depression. Am J Psychiatry 2001;158:906-12.
36. Sachs GS, Nierenberg AA, Calabrese JR, et al. Effectiveness of adjunctive antidepressant treatment for bipolar depression. N Engl J Med 2007;356:1711-22.
37. Sidor MM, MacQueen GM. Antidepressants for acute treatment of bipolar depression: a systematic review and meta-analysis. J Clin Psychiatry 2010 October 5 (Epub ahead of print).
38. Ghaemi SN, Wingo AP, Filkowski MA, Baldessarini RJ. Long-term antidepressant treatment in bipolar disorder: meta-analyses of benefits and risks. Acta Psychiatr Scand 2008;118:347-56.
39. Amsterdam JD, Shults J. Efficacy and safety of long-term fluoxetine versus lithium monotherapy of bipolar II disorder: a randomized, double-blind, placebo-substitution study. Am J Psychiatry 2010; 167:792-800.
40. Miklowitz DJ, Otto MW, Frank E, et al. Psychosocial treatments for bipolar depression: a 1-year randomized trial from the Systematic Treatment Enhancement Program. Arch Gen Psychiatry 2007;64: 419-26.
41. Truman CJ, Goldberg JF, Ghaemi SN, et al. Self-reported history of manic/hypomanic switch associated with antidepressant use: data from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). J Clin Psychiatry 2007;68:1472-9.
42. Vieta E, Martinez-Arán A, Goikolea JM, et al. A randomized trial comparing paroxetine and venlafaxine in the treatment of bipolar depressed patients taking mood stabilizers. J Clin Psychiatry 2002; 63:508-12.
43. Frye MA, Helleman G, McElroy SL, et al. Correlates of treatment-emergent mania associated with antidepressant treatment in bipolar depression. Am J Psychiatry 2009;166:164-72.
44. Frye MA, Grunze H, Suppes T, et al. A placebo-controlled evaluation of adjunctive modafinil in the treatment of bipolar depression. Am J Psychiatry 2007;164: 1242-9.
45. Goldberg JF, Burdick KE, Endick CJ. Preliminary randomized, double-blind, placebo-controlled trial of pramipexole added to mood stabilizers for treatment-resistant bipolar depression. Am J Psychiatry 2004;161:564-6.
46. Zarate CA Jr, Payne JL, Singh J, et al. Pramipexole for bipolar II depression: a placebo-controlled proof of concept study. Biol Psychiatry 2004;56:54-60.
47. Yatham LN, Kennedy SH, Schaffer A, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2009. Bipolar Disord 2009;11:225-55.