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When to suspect bipolar disorder

Bipolar disease is often misdiagnosed, sometimes repeatedly. The screening tool and tips you'll find here will help you identify patients without delay.

PRACTICE RECOMMENDATIONS

› *Before prescribing antidepressant therapy to depressed patients, screen for bipolar illness, either by taking a detailed medical and family history or by administering the Mood Disorder Questionnaire.* (A)

› *Be alert to medical and psychiatric comorbidities in patients with bipolar illness, particularly anxiety disorders and substance abuse.* (A)

› *Prescribe a mood stabilizer for acutely depressed patients with bipolar disorder; if the depression does not resolve, add an agent with relapse prevention properties.* (B)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence
(B) Inconsistent or limited-quality patient-oriented evidence
(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

As a family physician, you are better positioned than you might think to make a difference in the lives of patients with bipolar illness. Not only are you likely to be involved in monitoring such patients, but you may frequently be the first clinician patients with bipolar symptoms seek help from.

All it takes to provide that help is a heightened awareness of bipolar disorder, the ways in which bipolar patients present, and the signs and symptoms to look for. Yet evidence suggests that many physicians do not have adequate knowledge of this chronic and debilitating condition. While close to one-third of patients with bipolar disorder seek medical care within a year of the onset of bipolar symptoms, nearly 70% do not receive an accurate diagnosis until they have seen an average of 4 physicians.[1] Misdiagnosis—both underdetection[1] and over-inclusion[2]—often results in improper treatment. And even when the diagnosis is correct, patients with bipolar disease often receive inadequate or harmful treatment.[3]

Ongoing care for bipolar illness is best provided in collaboration with a psychiatrist. With the disorder affecting about 3% to 5% of the US population,[4] family physicians will inevitably play a key role in diagnosis and treatment. The text, tables, and screening tool that follow will help with both.

Bipolar diagnosis hinges on this characteristic

The *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, Text Revision (DSM-IV-TR) defines 4 types of bipolar illness: bipolar I, bipolar II, cyclothymia (the most mild form), and not otherwise specified (**TABLE 1**).[5] The key feature of all 4 types—and the distinguishing characteristic that diagnosis typically hinges on—is a manic or hypomanic episode (**TABLE 2**).[5]

Although a full-blown manic episode may not be hard to identify, hypomania is easily missed. By definition, hypomania—with its heightened sense of well-being and

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productivity—is not problematic and is rarely a patient's primary complaint.

Mixed mania, a feature of bipolar I, is the worst of both worlds: It is a state in which a full manic episode is superimposed on a full depressive episode—a depression with all the energy and force of a mania. Patients who have experienced one episode of mixed mania have a 12-fold increase in mixed states, 6.5 times more depression, and 1.7 times more dysthymia than those who experience manic episodes without the overlay of depression.[6]

Complicating matters: Numerous comorbidities

Bipolar illness predisposes patients to multiple medical and psychiatric comorbidities. Cardiovascular, cerebrovascular, and metabolic disorders and sleep disturbances are common in those with bipolar disorder.[7] So is obesity, which affects about 50% of patients with bipolar disease.[8]

Bipolar patients also suffer from an extremely high rate of comorbid psychiatric conditions. Overall, 93% of those with bipolar I also have an anxiety disorder, 71% suffer from drug or alcohol dependence, and 50% suffer from dysthymia, according to the National Comorbidity Survey.[9] In addition, about two-thirds of bipolar patients suffer from various personality disorders[10]—a comorbidity that is particularly disturbing because it is associated with a chronically dysfunctional pattern of problem-solving.

Even without comorbidities, the impact of bipolar disorder is significant: In a study of 1468 patients with bipolar disorder, complaints of difficulties with work, leisure activities, and family and social interactions were common.[11] Women were more likely to cite disruption of social and family life, while men often reported having been convicted of crimes. Younger patients reported a greater number of symptomatic days compared with their older counterparts.[11]

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TABLE 1
Types of bipolar disease: DSM-IV diagnoses[5]

Bipolar I	Bipolar II	Cyclothymia	Bipolar disorder not otherwise specified
≥1 manic or mixed lifetime episode, frequently accompanied by major depressive episodes	≥1 major depressive episode, accompanied by ≥1 lifetime hypomanic episode	≥2 years of numerous periods of hypomanic and subsyndromal depressive symptoms	Symptoms resemble, but do not meet, criteria for any specific bipolar disorder

The vast majority (93%) of patients with bipolar I disease also suffer from an anxiety disorder, and most (71%) have a substance abuse disorder.

Suicide risk. Patients with bipolar disorder also face an increased risk of suicide, particularly in the depressive phase of the illness. Among 12,662 Oregon Medicaid patients diagnosed with, and treated for, bipolar disorder between 1998 and 2003, there were 11 deaths by suicide and 79 significant suicide attempts.[12]

Suspect bipolar disorder?

One of the best ways by which family physicians can speed up and improve the accuracy of bipolar diagnosis is to utilize the Mood Disorder Questionnaire (MDQ) (**TABLE 3**).[13] Patients with any mood complaint are its target population. Within that group, the MDQ has been found to have excellent specificity (0.90) and acceptable sensitivity (0.73).[13] (For more on identifying patients with bipolar disease, see "A blood test for bipolar disorder?" on page 687.)

When to administer the MDQ

Because patients with bipolar disease are more likely to seek help when they are suffering from a depressive episode, it is important to maintain a high index of suspicion. Before ruling out bipolar disease, take a complete medical history, inquiring about comorbidities, family history, and whether the patient can recall any episodes of agitation, intense irritation, or other manifestations of mania or hypomania (**TABLE 2**).[5] If, based on the history, you continue to suspect bipolar disorder, administer the MDQ.

If the patient has a positive screen, your next step would be to initiate treatment for bipolar disorder, even if depression is the presenting symptom. A referral to a psychiatrist would be indicated, as well.

Complexities of bipolar treatment

In recent years, numerous agents have been approved by the US Food and Drug Administration (FDA) for the treatment of bipolar illness in general, and for acute mania in particular. Nearly all of the second-generation, or atypical, antipsychotics have been approved for use in acute mania.[14] (Mixed states should be treated the same as mania.) Most of these agents have also been found to be useful as maintenance medications, to prevent relapse (**TABLE 4**).

Considerable evidence suggests that lithium significantly reduces the risk of relapse, particularly in classic euphoric mania. Other agents that are approved for maintenance therapy include aripiprazole, lamotrigine, and olanzapine as monotherapy, and olanzapine, quetiapine, and ziprasidone as add-on agents to lithium or divalproex. Combining a mood stabilizer and an antipsychotic agent generally leads to better outcomes, both in acute mania[15] and relapse prevention,[16] compared with a mood stabilizer alone. However, bipolar depression, which is more common than either mania[17] or hypomania,[18] is the major clinical challenge.

What's best for bipolar depression?

For the acutely depressed bipolar patient, optimizing mood stabilization therapy is typically the first step. If the depression doesn't resolve in 4 or 5 weeks, adding an agent with relapse prevention properties is a preferred approach. Antidepressants may be harmful to patients with bipolar disorder (possibly triggering manic episodes, rapid cycling, or a chronic dysphoric state),[3,19] and are usually tried only after other options have been exhausted.

TABLE 2

Mania and hypomania: DSM-IV criteria[5]

To identify an episode of mania or hypomania, all of the following criteria must be met. Of note: Hypomania has the same criteria as mania, with 2 notable exceptions: (1) the minimum duration of hypomania is 4 days, rather than 7;* and (2) hypomania is not significantly problematic.

- Euphoric, expansive, or irritable mood (not due to drugs)
- 3 or 4 of the following (4 if irritable mood):
  - Reduced need for sleep
  - Increased goal-directed activity or agitation
  - Increased involvement in pleasurable, but potentially destructive, activity
  - Pressured speech
  - Distractibility
  - Flight of ideas/racing thoughts
  - Grandiose/increased self-esteem

*There is no maximal duration, but the average manic episode lasts 1 to 2 months.

Quetiapine, which is effective for the treatment of mania at doses around 600 mg daily, appears to also be effective for the treatment of acute bipolar depression at doses around 300 mg/d.[20] In 2-year studies in which quetiapine was added to either lithium or divalproex, the 2-drug combination was found to reduce the risk for relapse approximately 3-fold compared with the mood stabilizer alone.[16]

Olanzapine/fluoxetine. Besides quetiapine, this drug combination is the only other agent with FDA approval for the treatment of bipolar depression. A 24-week open extension trial found that the risk for a manic episode due to the coadministration of fluoxetine was low, but 27% of those studied relapsed into depression.[21]

Drugs that do not have FDA approval specifically for bipolar depression may also be used to treat it.

Lithium, which has antidepressant activity, particularly at levels exceeding 0.8 mEq/L, is one such drug. In addition to its effectiveness in treating bipolar depression, lithium appears to have an antisuicide effect.[12]

In a recent study of patients with bipolar disorder, lithium was found to be more protective than other mood stabilizers. The hazard ratio (HR) for suicide attempts was significantly greater for patients taking divalproex (HR=2.7; $P<.001$) or carbamazepine (HR=2.8; $P<.001$) compared with patients taking lithium.[12]

Modafinil, a nonstimulant used to increase alertness in patients with daytime sleepiness due to a variety of conditions, has been tested as an adjunctive agent in depressed bipolar patients. In a blinded study, patients were randomly assigned to have modafinil (n=41) or placebo (n=44) added to their existing treatment regimen.[22] Response, defined as ≥50% improvement in mood, occurred at twice the rate in those treated with modafinil (44%) compared with those on placebo (23%; $P<.05$).[22] In the brief (6 week) study, modafinil did not appear to cause an increase in manic or hypomanic episodes.[22]

Pramipexole, a dopamine agonist used for early-stage Parkinson's disease, has been tested in patients with bipolar depression in 2 small, short-term placebo-controlled trials. A total of 15 patients with type I disease and 28 patients with type II disease were studied for a 6-week period. The results: 60% to 67% of patients taking pramipexole responded, vs 9% to 20% of those on placebo.[23,24]

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Women with bipolar disorder typically report disruption of social and family life as a disturbing effect of the illness; men are more likely to report that they have been convicted of crimes.

TABLE 3

The Mood Disorder Questionnaire bipolar screening tool

Please answer each question to the best of your ability.

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 much 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?		
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		
Have any of your blood relatives (ie, children, siblings, parents, grandparents, aunts, uncles) had manic-depressive illness or bipolar disorder?		

For a positive screen, 7 of the 13 items in No. 1 must be Yes, No. 2 must be Yes, and No. 3 must be moderate or serious.

Source: Hirschfeld RM, et al. *Am J Psychiatry*. 2000.[13] Reprinted with permission.

Combining a mood stabilizer and an antipsychotic generally results in better outcomes than a mood stabilizer alone for both acute mania and relapse prevention.

Electroconvulsive therapy (ECT) is an underutilized treatment that is effective for depressed patients who are resistant to pharmacological treatment. In fact, bipolar depression may improve more rapidly than unipolar depression with ultra-brief pulse treatment—a therapy in which the pulse width of the electrical stimulus is much briefer (<0.5 msec) than that of standard ECT.[25] ECT has also been shown to be effective for mixed states, in which depression and mania coexist.[26] The cognitive adverse effects associated with ECT can be reduced while maintaining the same efficacy by using bifrontal

A blood test for bipolar disorder?

Although the DSM-IV identifies bipolar disorder on the basis of symptoms, there have been increasing attempts to diagnose the disease biologically. Most have been unsuccessful. However, an initial study found that a recently developed blood test (PsychNostics LLC, Baltimore, Md; http://psychnostics.com) that uses the membrane potential as a biological marker had a specificity of 0.88 and a sensitivity of 0.78. The blood test is a promising approach, but is still not ready for prime time.[31]

(instead of the typical bitemporal) electrode replacement.[27]

Predicting the course of disease, preventing relapse

Generally, the polarity of the current episode predicts that of future episodes. Studies have found that, independent of whether patients were on effective mood-stabilizing agents or placebo, those who relapsed had an episode like their most recent one by a ratio of more than 2 to 1.[28]

Research suggests a link between age at onset of illness and cycling time and response to particular agents. In 1 trial, those with early-onset bipolar disorder (in adolescence) had briefer euthymic periods and responded better to carbamazepine compared with those who developed symptoms of bipolar disorder at a later age.[29] Late-onset bipolar illness (in the 30s or older) was characterized by longer euthymic periods and manic episodes that responded well to lithium.[29] The average age of onset is about 25 years.[30]

Regardless of patient age or age of onset of symptoms, however, prevention of relapse is the goal of ongoing treatment. You can help by as-

In addition to having antidepressant qualities, lithium appears to have an antisuicide effect.

TABLE 4
FDA-approved treatments for bipolar disorder[32,33]

Treatment	Mania	Bipolar depression	Maintenance
Aripiprazole	√		√
Asenapine	√		
Carbamazepine ER	√		
Chlorpromazine	√		
Divalproex; divalproex ER	√		
Lamotrigine			√
Lithium	√*		√
Olanzapine	√	√†	√
Quetiapine; quetiapine XR	√	√	√
Risperidone	√		
Ziprasidone	√		√

ER, extended release; FDA, US Food and Drug Administration; XR, extended release.
*Not approved for mixed mania.
†Approved for bipolar depression in combination with fluoxetine.

sessing the patient's mood, reviewing the medication regimen and level of compliance, and offering support at every visit—and by consulting with the patient's psychiatrist, as needed. JFP

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Studies have found that patients who relapsed had an episode like their most recent one by a ratio of more than 2 to 1.

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