# Recognizing and Treating Bipolar Disorder

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All physicians need to be familiar with the diagnosis and treatment of mood disorders. Fifty percent of all depressive episodes are treated in a primary care setting rather than by psychiatrists.[1] Bipolar disorder is a complex illness that is frequently misdiagnosed as unipolar depression,[2,3] which often results in patients not receiving appropriate treatment.[2] Further, patients may actually receive treatments, such as antidepressants, that can worsen their condition.[2,4] Therefore, primary care physicians must know how to accurately assess patients with mood disorders. Specifically, they must be able to diagnose and, in some cases, treat bipolar disorder. Finally, there is a high risk of suicide among patients with bipolar disorder.[2] All patients with bipolar disorder or unipolar depression must be carefully evaluated for risk of self-harm.

Many clinicians think of bipolar disorder as an illness that presents with classic manic symptoms of euphoria, grandiosity, and high energy; is easily recognizable; and frequently results in psychiatric hospitalization. Although some bipolar patients do experience full manic episodes, the disorder actually comprises a spectrum of abnormal mood states.[2,5] These include mania, hypomania, depression, mixed states, and hyperthymic temperament.[2] With the exception of mania, these states are frequently difficult for physicians to recognize as bipolar disorder, often resulting in misdiagnosis.

This article reviews the definitions of bipolar disorder and discusses barriers to accurate diagnosis. The assessment of patients presenting with possible bipolar disorder and current treatment recommendations also are reviewed.

## DEFINITIONS OF BIPOLAR DISORDER

The Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM-IV-TR), describes 3 types of manic episodes. **Table 1** lists specific symptoms seen during these states, which are called manic, hypomanic, and mixed episodes.[5] All require an abnormally elevated, expansive, or irritable mood. Associated symptoms are grandiosity, decreased need for sleep, increased speech, flight of ideas or racing thoughts, distractibility, increased activity, and excessive involvement in pleasurable activities.

The DSM-IV-TR describes 4 subtypes of bipolar disorder that are based upon the existence and severity of manic, mixed, and depressive episodes.[5] The subtypes are bipolar I disorder, bipolar II disorder, cyclothymic disorder, and bipolar disorder not otherwise specified (NOS). Bipolar I disorder requires at least 1 manic or mixed episode, whereas bipolar II describes patients who have had major depression and hypomania. Cyclothymic disorder indicates periods of hypomania as well as milder depressive symptoms. **Table 2** provides a summary of DSM-IV-TR manic, hypomanic, and depressive episode criteria for the bipolar and depressive disorders.[5]

Many experts believe that the current DSM-IV-TR diagnostic criteria for bipolar disorders are too restrictive and do not capture the full spectrum of the illness.[2,4,6] More inclusive definitions have been proposed. Young and Klerman[7] have proposed 6 subtypes of bipolar illness. Their classification includes antidepressant-induced manic symptoms, which DSM-IV-TR criteria exclude, as well as major depression in individuals with a family history of bipolar illness.[7] Another classification system has been proposed by Akiskal and Pinto[8] that also includes medication-induced manic episodes as well as the concept of hyperthymic temperament. Hyperthymic temperament describes individuals who are overconfident, cheerful, extroverted, high energy, and stimulus-seeking. Ghaemi and colleagues[4] have suggested a definition of bipolar spectrum disorder that takes into account family history, antidepressant-induced mania, and other symptoms thought to suggest bipolarity in depressed patients. These alternative classification systems suggest that clinicians must take into account presentations not specified in the DSM-IV-TR when evaluating patients with mood symptoms.

## DELAYED AND MISSED DIAGNOSIS

There is strong evidence that bipolar disorder is frequently underdiagnosed. Ghaemi and colleagues found a 40% rate of bipolar disorder misdiagnosed as unipolar depression in hospitalized patients.[4] Several

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**Table 1.** Symptoms of Manic, Hypomanic, and Mixed States

| Diagnostic Criteria | Manic Episode | Hypomanic Episode | Mixed Episode |
|---|---|---|---|
| Mood state | Elevated or irritable | Same as for manic episode | Same as for manic episode<br>Coexisting depression |
| Associated symptoms (3 required or 4 if the mood is irritable but not elevated) | Grandiosity<br>Decreased sleep<br>Increased speech<br>Flight of ideas<br>Distractibility<br>Increased activity<br>Excessive pleasure-seeking | Same as for manic episode | Same as for manic episode<br>Also meets criteria for a major depressive episode |
| Duration of episode required for diagnosis | 1 week or hospitalization | At least 4 days | At least 1 week |
| Impairment | Marked impairment or hospitalization or psychosis | Does not cause marked impairment | Same as for manic episode |

Data from American Psychiatric Association. Mood disorders. In: Diagnostic and statistical manual of mental disorders. 4th ed, text revision. Washington (DC): The Association; 2000:345–428.

**Table 2.** Mood Disorder Episode Criteria

| Disorder | Depressive Episodes | Manic or Mixed Episodes | Hypomanic Episodes |
|---|---|---|---|
| Bipolar I disorder | Common but not required | ≥ 1 required | Common but not required |
| Bipolar II disorder | ≥ 1 required | None allowed | ≥ 1 required |
| Cyclothymic disorder | Required, but not major depression | None allowed | Numerous periods over 2 years required |
| Bipolar disorder NOS | Common but not required | None allowed | Required, but do not meet criteria for a specific bipolar disorder |
| Major depressive disorder | ≥ 1 required | None allowed | None allowed |
| Dysthymic disorder | ≥ 2 years required but not major depression | None allowed | None allowed |

NOS = not otherwise specified.

Data from American Psychiatric Association. Mood disorders. In: Diagnostic and statistical manual of mental disorders. 4th ed, text revision. Washington (DC): The Association; 2000:345–428.

other studies reviewed in the report by Ghaemi et al also suggest that the misdiagnosis of bipolar disorder as unipolar depression may be common. At least 2 studies have found that 34% of patients with this illness wait at least 10 years after symptom onset before a diagnosis of bipolar disorder is given.[2,9]

The delay in receiving an accurate diagnosis has a substantial adverse result for many bipolar patients.[2] One outcome is that these individuals do not receive treatment that adequately controls their symptoms. Another result of misdiagnosis that is even more concerning is that many patients receive antidepressants for what is thought to be unipolar depression.[2,4] This can lead to a worsening of mood cycling and exacerbation of manic symptoms.[4]

The most serious outcome of untreated bipolar disorder is suicide.[2] Goodwin and Jamison reported a mean suicide rate of 18.9% among bipolar patients.[10] The greatest risk of suicide is during depressive episodes. Isometsa and colleagues found that 79% of

**Table 3.** Assessment of Patients with Mood Symptoms

| |
|---|
| Obtain symptoms and duration of current manic or depressive episode |
| Inquire about past manic, hypomanic, or depressive episodes |
| Assess for substance abuse |
| Determine if there is a family history of mood disorders |
| Ask about past treatment with psychiatric medications and response |
| Evaluate for risk of harm to self or others |

**Table 4.** Factors That May Increase the Suicide Risk in Bipolar Disorder

| |
|---|
| Being single |
| Comorbid eating, anxiety, or personality disorder |
| Family history of suicide |
| History of physical or sexual abuse |
| Lack of medical insurance |
| Less education |
| Loss of significant other |
| Lower income |
| Severe depression |
| Single motherhood |

Adapted from Post RM. New findings on suicide attempts, substance abuse, obesity and more. Curr Psychiatry 2002;1:26–32.

bipolar patients who committed suicide did so during an episode of major depression, whereas only 11% did so during either a manic or hypomanic episode.[11]

## BARRIERS TO ACCURATE DIAGNOSIS

Several factors have contributed to the misdiagnosis of bipolar spectrum disorders.[2,6] In the past, bipolar disorder was thought to be relatively rare as compared to unipolar depression. It is well documented that major depression is a common condition, with a lifetime prevalence of 21.3% for females and 12.7% for males in the United States.[12] The DSM-IV-TR indicates that the lifetime prevalence of bipolar I disorder is between 0.4% to 1.6% and about 0.5% for bipolar II disorder.[5] However, a review of 6 recent studies reveals a much higher lifetime prevalence of bipolar spectrum illness, ranging from 3.0% to 8.8%.[13] Currently, experts believe the actual prevalence of all bipolar disorders is between 2% to 7% in the United States.[14,15] It is likely that bipolar disorder has been underdiagnosed in part because it was thought to be a rare condition and clinicians have not expected that it would exist in many patients who present with depressive symptoms.[6]

Another factor contributing to misdiagnosis is that virtually all bipolar patients experience long periods of depression.[6] Depression almost always causes more subjective distress than mania. This results in patients seeking help when they are depressed rather than manic. In addition, patient insight is more impaired in mania than in depression, thus reliance on patients' self-report about their own manic symptoms is thought to contribute to underdiagnosis of mania. Furthermore, physicians often do not ask their depressed patients about the possibility of having manic symptoms.[2]

The diagnostic criteria for bipolar disorder are relatively complicated. One study found that psychiatrists have much more difficulty recalling the diagnostic criteria for bipolar disorder as compared to unipolar depression.[6] This confusion may result in clinicians being less likely to evaluate patients for the possibility of bipolar disorder.

Finally, there has been an increased interest in depressive disorders in recent years. This has been accompanied by greater availability and marketing of numerous antidepressant agents. It has been hypothesized that these factors may have contributed to an increase in the diagnosis of unipolar depression without a corresponding increase in the awareness of bipolar spectrum illness.[4]

## EVALUATING PATIENTS WITH MOOD SYMPTOMS

**Table 3** outlines the evaluation of patients with mood symptoms. An accurate diagnostic assessment requires careful and thorough attention to the clinical history.[16–18] The clinician must inquire about the severity, duration, and specific symptoms of the current episode, regardless of whether the patient presents with depression or mania. Next, the physician must determine whether there have been prior episodes of either mania or depression. A detailed family psychiatric history must be obtained to assess whether the patient has a genetic risk for unipolar depression, bipolar spectrum illness, or both. Also, it is critical to assess whether the patient has any comorbid psychiatric conditions, such as an anxiety disorder or substance abuse. Finally, a careful evaluation of the patient's risk of harming self or others must be completed. Several factors have been identified that appear to increase the risk of suicide in bipolar disorder (**Table 4**).[19] If it is determined that the patient is unsafe, hospitalization or an emergency consultation with a mental health professional is indicated.

It is critical to carefully evaluate all patients who seek

**Table 5.** Presentation of Depressed Patients Who May Be Bipolar

| |
|---|
| Hyperphagia/weight gain |
| Hypersomnia |
| Melancholic features |
| Severe anhedonia |
| Seasonal mood changes |
| Psychomotor slowing |
| Psychotic features |
| History of poor response to antidepressants |
| History of recurrent but brief depressive episodes |
| History of antidepressant-induced mania or hypomania |
| Family history of bipolar illness in a first-degree relative |
| Early age of onset |
| Postpartum onset |

**Table 6.** Features That May Indicate a Mixed Episode

| |
|---|
| Anxiety and panic |
| Extreme fatigue |
| Family history of bipolar illness in a first-degree relative |
| Psychomotor agitation |
| Racing thoughts |
| Severe insomnia |
| Severe irritability |
| Suicidal ideation |

treatment for depression to rule out bipolar spectrum illness. During the assessment of depressed patients, physicians should keep in mind 3 categories of patients who may be bipolar but are not currently manic. The first is individuals who are at high risk for developing bipolar illness but have not yet had any manic or hypomanic symptoms. The second group consists of those who have had abnormal mood elevation but have not been diagnosed with bipolar disorder. Finally, some patients who report depression are actually experiencing a mixed state.[2,15] A number of clinical clues can help identify patients in each category. Patients with bipolar depression without previous manic or hypomanic episodes or those who have had undiagnosed episodes frequently experience certain features that may help differentiate them from patients with unipolar depression (**Table 5**).[4,6,20] Clues to a mixed episode are listed in **Table 6**.

**Table 7.** Resources for Patients with Bipolar Disorder

| | |
|---|---|
| Depression and Bipolar Support Alliance | |
| (800) 826-3632 | www.DBSAlliance.org |
| National Alliance for the Mentally Ill | |
| (800) 950-6264 | www.nami.org |
| Child & Adolescent Bipolar Foundation | |
| (847) 256-8525 | www.bpkids.org |
| American Foundation for Suicide Prevention | |
| (888) 333-2377 | www.afsp.org |
| American Psychiatric Association | |
| (888) 357-7924 | www.psych.org |
| American Psychological Association | |
| (800) 374-2721 | www.helping.apa.org |

Because of the difficulty of detecting bipolar spectrum illness in patients who present with depression, the utilization of brief screening instruments can be helpful.[2,6,18] The Mood Disorder Questionnaire (MDQ), which was developed by Hirschfeld and colleagues, is one such instrument.[2,18] The instrument is a validated self-reported, single page, paper-and-pencil inventory that can be completed in a few minutes by patients.[2] Scoring is straightforward and can be accomplished by a physician, nurse, or medical assistant. In addition to completing the MDQ in doctor's offices, patients can access it on the web site of the Depression and Bipolar Support Alliance (www.dbsalliance.org).

## THERAPEUTIC AGENTS FOR TREATMENT OF BIPOLAR DISORDER

The choice of appropriate treatment depends on several factors, including whether the current episode is manic, mixed, or depressed; the severity of current symptoms; the cycling pattern; and finally, past treatment response. In all cases, patient education and support are essential components of treatment. **Table 7** lists patient information and support resources.

Several evidence-based psychotherapies have been developed specifically for bipolar disorder.[21–23] These have been shown to decrease the risk of relapse when used in conjunction with pharmacologic interventions. Therefore, referral to a psychotherapist familiar with these modalities should be considered as part of the overall treatment plan. In addition, clinicians must always assess patients with mood disorders for suicidal ideation (Table 4).

The medication classes currently used to treat bipolar disorder are mood stabilizers, atypical antipsychotics, antidepressants, and benzodiazepines. A number of

**Table 8.** Mood Stabilizers Used for Acute Mania

| Medication | Starting Dose | Usual Daily Dose | Plasma Levels | Monitoring |
|---|---|---|---|---|
| Lithium | 300 mg tid | 900–1800 mg | 1.0–1.5 mEq/L (acute mania)<br>0.4–0.8 mEq/L (maintenance) | Lithium level, thyroid and renal function |
| Valproate | 250 mg tid (loading dose up to 20 mg/kg daily) | 750–2500 mg | 50–125 μg/mL | Valproate level, hepatic and hematologic function |
| Carbamazepine | 200 mg bid or tid | 400–1600 mg | 4–12 μg/mL | Carbamazepine level, hepatic and hematologic function |

bid = twice daily, tid = 3 times daily.

Data from Sadock BJ, Sadock VA. Kaplan and Sadock's synopsis of psychiatry: behavioral sciences/clinical psychiatry. 9th ed. Philadelphia: Lippincott, Williams & Wilkins; 2003:974–1150.

medications from these classes are in common clinical use, but only 4 medications have US Food and Drug Administration (FDA) approval for the treatment of adult bipolar disorder. These are lithium, lamotrigine, valproate, and olanzapine.

### Mood Stabilizers

The mood stabilizers include lithium and several anticonvulsant agents that have been found to be effective for bipolar disorder. **Table 8** provides a comparison of the 3 mood stabilizers most frequently used for the treatment of acute mania.

Lithium has historically been considered the gold standard for the treatment of bipolar disorder. However, the exact mechanism of action for this agent remains unclear.[24] Recent research suggests that it is unlikely that lithium modulates neurotransmission at the level of the synapse. Currently, attention has been focused on the possibility that lithium exerts its therapeutic action via modulation of postreceptor signal transduction mechanisms.[24] Lithium works preferentially for classic, euphoric mania and is typically less effective for patients with rapid cycling and those with mixed depression and mania.[25]

Lithium has a number of potential side effects that can limit its useful, including thirst, polyuria, tremor, memory loss, weight gain, diarrhea, impairment of renal tubular function, hypothyroidism, and benign leukocytosis.[25] There is a risk of birth defects if administered to pregnant women during the first trimester of pregnancy. Finally, lithium toxicity is a risk, and overdose can be fatal. Plasma concentration monitoring, along with routine laboratory studies, are required during lithium treatment.

The anticonvulsant mood stabilizers are valproate, carbamazepine, lamotrigine, and oxcarbazepine. Two other anticonvulsant agents that have received considerable attention as potential antimanic drugs are gabapentin and topiramate. Although results of initial open-label trials for both agents were promising, controlled trials have not shown either agent to be effective for mania.[26] However, limited data support the effectiveness of topiramate for bipolar depression.[27]

As with lithium, the mechanism of action of the anticonvulsants in bipolar disorder is not well understood. Most have multiple biochemical effects that reduce central nervous system excitation or increase inhibition mechanisms.[25] It is likely that these mechanisms underlie both the anticonvulsant and antimanic effects of these agents.

Valproate is effective for both acute and maintenance treatment of bipolar disorder.[25] It is more effective than lithium for the treatment of rapid cycling bipolar disorder and mixed depression and mania. Common adverse effects of valproate include nausea, sedation, tremor, hair loss, and weight gain. More serious adverse effects are thrombocytopenia, agranulocytosis, pancreatitis, and fatal hepatotoxicity.[25] There also is a possible association with polycystic ovarian syndrome.[18] Valproate should not be used by pregnant women as it is associated with neural tube defects such as spina bifida. Finally, overdose can be fatal. Plasma concentration monitoring and routine laboratory studies are required during valproate treatment.

Carbamazepine is recommended as an alternative to lithium and valproate for the treatment of bipolar mania.[18] Common side effects include diplopia, blurred vision, fatigue, nausea, weight gain, and ataxia. Less common side effects are mild leukopenia, mild

thrombocytopenia, hyponatremia, and liver enzyme elevations. Serious and potentially fatal side effects of carbamazepine include agranulocytosis, aplastic anemia, thrombocytopenia, hepatic failure, exfoliative dermatitis, and pancreatitis. Overdose may be fatal. Carbamazepine has many potential drug interactions and may decrease the reliability of contraceptives. There is some evidence of an association between use of carbamazepine during pregnancy and congenital malformations.[25]

Oxcarbazepine is a congener of carbamazepine that has fewer potential side effects. Small studies have suggested efficacy for acute mania but more rigorous studies are needed to clearly establish the role of this agent for the treatment of bipolar disorder.[26]

Lamotrigine has been evaluated in both open and controlled studies as a treatment for acute mania.[28] One open study and one controlled study suggested some benefit; however, the other two controlled studies were negative. Therefore, lamotrigine is not currently recommended as a treatment for acute bipolar mania.[28] Lamotrigine has been shown to be effective for preventing relapse of rapid cycling bipolar illness[28] and recently received FDA approval for maintenance therapy of bipolar I disorder.

Lamotrigine is effective for bipolar depression and is recommended as a first-line treatment for acute depression in bipolar disorder.[18,28] Common side effects of lamotrigine are headache, nausea, infection, and xerostomia.[18] There is also a risk of serious rash, including Stevens-Johnson syndrome and toxic epidermal necrolysis.[18] The risk of serious rash can be minimized by initiating treatment at low doses that are increased slowly.[18,28] Initial doses must be lower in patients who are also receiving valproate.

### Atypical Antipsychotic Agents

Atypical antipsychotic agents are used to treat mania and psychotic symptoms associated with bipolar disorder. There is emerging evidence that these agents also may be effective for bipolar depression.[29]

Atypical antipsychotic agents are frequently indicated in the treatment of bipolar disorder because psychotic symptoms occur in 90% of bipolar patients at some point during the course of their illness. Patients with psychotic features typically require treatment with an antipsychotic agent, either as monotherapy or in combination with another mood stabilizer.[18] When antipsychotic agents are used, the atypical agents are preferred over conventional antipsychotic agents because of their more benign side effect profile.[18] Also, there is some evidence that conventional antipsychotic agents may induce depression in bipolar patients.[30]

Atypical antipsychotic agents are increasingly being used to treat bipolar mania.[26] Olanzapine is the only antipsychotic agent that is currently FDA approved for the treatment of mania. It has been shown to be superior to placebo in the treatment of acute bipolar mania in 2 large multicenter randomized controlled trials.[31,32] Other studies have found that it is comparable in efficacy to lithium, valproate, and haldol.[18]

Although olanzapine is the only atypical antipsychotic agent with FDA approval for the treatment of mania, there is strong evidence that the other atypical agents also are effective.[26] Several open label studies have demonstrated antimanic properties of clozapine.[26] Risperidone has been studied in 2 randomized controlled trials, both of which demonstrated effectiveness.[33,34] A controlled study of ziprasidone has demonstrated antimanic properties.[35] A controlled study of Aripiprazole demonstrated effectiveness for treatment of acute mania.[36] Quetiapine has shown effectiveness for the treatment of mania in several case series and open trials.[26] One randomized controlled trial has demonstrated the effectiveness of quetiapine as an adjunctive treatment for adolescent mania.[37] Further, 2 large safety and efficacy trials of quetiapine in adult bipolar disorder have been completed. A 12-week, multicenter, double-blind, placebo-controlled study demonstrated that this agent is effective as monotherapy for mania.[38] Another multicenter, randomized controlled study demonstrated effectiveness as add-on therapy with lithium or divalproex for acute mania.[39]

The atypical antipsychotic agents are less likely than conventional antipsychotic agents to cause treatment-emergent motor side effects.[25] With the exception of clozapine, however, all are believed to have some risk for causing tardive dyskinesia. Weight gain is a common side effect, which is most likely with olanzapine and clozapine, and least likely with ziprasidone and aripiprazole.[25] Hyperlipidemia and new-onset diabetes are possible weight-related adverse effects.[25] Ziprasidone may lead to significant electrocardiographic changes in susceptible patients and clozapine treatment is associated with agranulocytosis. Finally, hyperprolactinemia is a potential side effect most strongly associated with risperidone.[25]

### Antidepressants

For patients with a known history of manic, hypomanic, or mixed symptoms, the treatment of depressive episodes is substantially different than for patients with unipolar depression. Antidepressant monotherapy is not recommended because of the risk of causing a switch into mania. If antidepressants are used, they should be used in combination with a mood stabilizer.

**Table 9.** Management of Bipolar Depression

| Presentation of Depressive Symptoms | Interventions |
|---|---|
| Breakthrough depressive episode and currently on mood stabilizers | Optimize dose/blood level of maintenance medications<br>Consider adjunctive psychotherapy<br>If no or incomplete response, then follow guidelines below |
| Acute depressive episode | Lithium or lamotrigine monotherapy is first-line treatment<br>Antidepressant monotherapy not recommended<br>Lithium in combination with an antidepressant is an alternative, especially for more seriously ill patients<br>If no response, add lamotrigine, bupropion, or an SSRI<br>Consider adjunctive psychotherapy |
| Severe refractory depression with suicidal ideation and/or psychosis | Electroconvulsive therapy |
| Psychotic depression | Augment with atypical antipsychotic agent<br>Electroconvulsive therapy may be necessary if no response |

SSRI = selective serotonin reuptake inhibitor.

Adapted from: Practice guideline for the treatment of patients with bipolar disorder. In: American Psychiatric Association. American Psychiatric Association practice guidelines for the treatment of psychiatric disorders compendium 2002. Washington (DC): The Association; 2002:547–634.

It is unclear which antidepressants are most effective in this setting.[29] Furthermore, it has not been established which are more likely to worsen mood cycling. However, there is some evidence that bupropion and the selective serotonin reuptake inhibitors are less likely to induce mania than tricyclic antidepressants or monoamine oxidase inhibitors.[29]

### Benzodiazepines

Benzodiazepines have a limited role as an adjunctive treatment in bipolar disorder.[18] Several studies have evaluated clonazepam and lorazepam for the treatment of acute bipolar mania. Interpretation of these studies is difficult because of multiple confounding factors.[18] However, the sedating effects of these agents may be beneficial during acute manic episodes when used as an adjunctive treatment to a primary mood stabilizer. Lorazepam is well absorbed when used intramuscularly, making it particularly useful for the management of agitated patients.[18] Because of the risk of abuse and dependence, these agents should generally only be used short term while waiting for the primary mood stabilizer to take effect.

## MANAGEMENT OF DEPRESSIVE EPISODES

The role of antidepressants in the treatment of bipolar depression is unclear because of a lack of controlled studies.[29] The treatment of depressive episodes in patients with bipolar disorder is substantially different than treatment of patients with unipolar depression. Not only must the physician focus on symptom control, but he or she also must avoid the precipitation of a manic or hypomanic episode. The management of bipolar depression is summarized in **Table 9**. The American Psychiatric Association[1] (APA) practice guideline for treatment of bipolar disorder recommends that either lithium or lamotrigine should be the first-line pharmacologic intervention.[18] Antidepressant monotherapy is not recommended because of the risk of inducing mania. Antidepressants should be used in combination with a mood stabilizer. Psychotherapy strategies, particularly interpersonal therapy and cognitive behavior therapy, may be beneficial along with medication. In severe cases, electroconvulsive therapy may be considered. Adult bipolar disorder is often comorbid with alcohol or other substance abuse.[40] Formal substance abuse treatment may be required in these cases.

Like those suffering from unipolar depression, patients with bipolar depression are at a high risk of suicide.[17,18] One study of adult bipolar I patients found that more than 50% had attempted suicide.[41] Suicide attempts had occurred during depressive episodes in 93% of these cases. Therefore, clinicians must carefully evaluate depressed bipolar patients for suicide risk and if necessary consider hospitalization or an emergency consultation with a psychiatrist.

The best approach to the treatment of depression for persons with suspected bipolar depression is not

**Table 10.** Pharmacologic Treatment of Bipolar Mania

| Mood State and/or Cycling Pattern | Pharmacologic Intervention |
|---|---|
| Severe mania | Lithium or valproate plus an atypical antipsychotic agent<br>Discontinue antidepressants if possible |
| Mild mania or hypomania | Lithium, valproate or atypical antipsychotic monotherapy<br>Discontinue antidepressants if possible |
| Rapid cycling pattern | Valproate or lamotrigine<br>Discontinue antidepressants if possible |
| Mixed mania and depression | Valproate monotherapy or, if severe, in combination with an atypical antipsychotic agent<br>Discontinue antidepressants if possible |
| Refractory mania | Clozapine or electroconvulsive therapy<br>Discontinue antidepressants if possible |
| Psychotic mania | Atypical antipsychotic monotherapy or in combination with a mood stabilizer<br>Discontinue antidepressants if possible |

Adapted from Practice guideline for the treatment of patients with bipolar disorder. In: American Psychiatric Association. American Psychiatric Association practice guidelines for the treatment of psychiatric disorders compendium 2002. Washington (DC): The Association; 2002:547–634.

well established. However, the first step is to screen for the possibility of bipolar disorder in patients presenting with symptoms of depression. This can be accomplished by asking specifically about symptoms and features outlined in Tables 5 and 6 and by using a diagnostic instrument such as the MDQ.

For patients who have not been diagnosed with bipolar disorder but have strong evidence suggestive of bipolar spectrum illness, antidepressants should be avoided or only used in combination with a mood stabilizer.[4,6] If the depression is mild, psychotherapy alone may be considered. For moderate or severe depression, then either mood stabilizer monotherapy or an antidepressant in combination with a mood stabilizer should be considered.

## MANAGEMENT OF MANIC SYMPTOMS

Patients with severe manic or mixed symptoms require prompt pharmacologic intervention. Some may require immediate hospitalization to prevent harm to self or others. If possible, an emergency consultation with a psychiatrist should be considered. **Table 10** provides an overview of the pharmacologic treatment of manic symptoms.

The APA practice guideline for the treatment of patients with bipolar disorder states that the first-line treatment for a severe manic or mixed episode is the initiation of combination therapy with lithium plus an antipsychotic agent, or valproate plus an atypical antipsychotic agent.[18] For less ill patients, monotherapy with lithium, valproate, or an atypical antipsychotic may be sufficient. Benzodiazepines may be used as short-term adjunctive treatment.[18]

Patients who have a current mixed presentation or rapid cycling warrant some additional considerations. Mixed depressive and manic symptoms may occur in approximately 30% of adult bipolar patients but ranges from 5% to 70% have been described.[42] If the current episode is mixed, valproate is generally preferred over lithium.[18,43,44]

Rapid cycling is defined by the DSM-IV-TR as the occurrence of 4 or more mood disturbances within a single year that meet criteria for a major depressive, mixed, manic, or hypomanic episode.[5] Rapid cycling is thought to occur in 14% to 24% of adult patients with bipolar disorder.[45] Depression is considered to be the hallmark of rapid cycling bipolar disorder.[46] Adults with rapid cycling frequently have greater length and severity of depressive episodes than those with non-rapid cycling illness.[47] In adults with bipolar illness, rapid cycling often occurs late in the course of the illness, is more common in females than males, is more commonly associated with bipolar II than bipolar I disorder, and seems to be destabilized by antidepressant use.[48] The APA guideline recommends lithium or valproate as the initial treatment for rapid cycling, with lamotrigine as an alternate.[18] Also, it recommends tapering antidepressants if possible. There is evidence that valproate and lamotrigine seem to be the most effective for rapid cycling in adults, but frequently require augmentation with lithium, carbamazepine, or an atypical antipsychotic agent.[49]

## MAINTENANCE TREATMENT

The goal of maintenance treatment in bipolar disorder is to prevent recurrence of both manic and depressive episodes. It is well established that long-term treatment is necessary for this illness. In contrast to acute treatment, however, there is much less evidence concerning the long-term effectiveness of most agents.[50] Lithium and lamotrigine have the most evidence for efficacy as maintenance treatments, but there is evidence to support the use of valproate, carbamazepine, and the atypical antipsychotic agents.[50] The most common clinical practice is to continue the agent or agents that were initially effective to control an acute episode. Until more results of long-term bipolar treatment studies are available, this is generally a sound approach and frequently involves combination treatment with 2 or more agents. However, once mood stabilization has been achieved, clinicians should consider whether medication adjustments are warranted either to decrease the risk of potential side effects or to initiate an agent with greater evidence for prevention of relapse. Finally, utilization of an evidence-based psychotherapy approach as an adjunctive treatment may further decrease the risk of relapse.[21–23]

## CONCLUSION

Bipolar disorder is a complex illness that can be difficult to diagnose and challenging to treat. However, recent advances in our understanding of the complex genetic and neurobiological etiologies of this illness hold promise for the future. Evidence-based pharmacologic and psychotherapeutic treatment strategies are being developed at a rapid pace and should greatly enhance our ability to manage this illness.

There is strong evidence that bipolar disorder is more prevalent than previously thought and that it is underdiagnosed. Furthermore, the evidence suggests that many patients receive antidepressants that can worsen the course of their illness when, in fact, a mood stabilizer is more appropriate treatment. These patients can be challenging not only for primary care physicians but also for psychiatrists. With a thorough evaluation, however, appropriate treatment decisions can be made and suffering alleviated for patients with bipolar disorder. **HP**

## REFERENCES


1. Docherty JP. Barriers to the diagnosis of depression in primary care. J Clin Psychiatry 1997;58 Suppl 1:5–10.
2. Hirschfeld RM. Bipolar spectrum disorder: improving its recognition and diagnosis. J Clin Psychiatry 2001;62 Suppl 14:5–9.
3. Ghaemi SN, Sachs GS, Chiou AM, et al. Is bipolar disorder still underdiagnosed? Are antidepressants overutilized? J Affect Disord 1999;52:135–44.
4. Ghaemi SN, Ko JY, Goodwin FK. The bipolar spectrum and the antidepressant view of the world. J Psychiatr Pract 2001;7:287–97.
5. American Psychiatric Association. Mood disorders. In: Diagnostic and statistical manual of mental disorders. 4th ed, text revision. Washington (DC): The Association; 2000:345–428.
6. Pies R. The "softer" end of the bipolar spectrum. J Psychiatr Pract 2002;8:189–95.
7. Young RC, Klerman GL. Mania in late life; focus on age at onset. Am J Psychiatry 1992;149:867–76.
8. Akiskal HS, Pinto O. The evolving bipolar spectrum. Prototypes I, II, III, and IV. Psychiatr Clin North Am 1999;22:517–34, vii.
9. 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;31:281–94.
10. Goodwin FK, Jamison KR. Manic-depressive illness. New York: Oxford University Press; 1990:227–44.
11. Isometsa ET, Henriksson MM, Aro HM, Lonnqvist JK. Suicide in bipolar patients in Finland. Am J Psychiatry 1994;151:1020–4.
12. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results for the National Comorbidity Survey. Arch Gen Psychiatry 1994;51:8–19.
13. Angst J. The emerging epidemiology of hypomania and bipolar II disorder. J Affect Disord 1998;50:143–51.
14. Goodwin FK, Ghaemi SN. The difficult-to-treat patient with bipolar disorder. In: Dewan MJ, Pies RW, editors. The difficult-to-treat psychiatric patient. Washington (DC): American Psychiatric Publishers; 2001:7–39.
15. Akiskal HS. The prevalent clinical spectrum of bipolar disorders: beyond DSM-IV. J Clin Psychopharmacol 1996;16(2 Suppl 1):4S–14S.
16. Practice guideline for the psychiatric evaluation of adults. In: American Psychiatric Association. American Psychiatric Association practice guidelines for the treatment of psychiatric disorders compendium 2002. Washington (DC): The Association; 2002:1–28.
17. Practice guideline for the treatment of patients with major depressive disorder. In: American Psychiatric Association. American Psychiatric Association practice guidelines for the treatment of psychiatric disorders. Compendium 2002. Washington (DC): The Association; 2002:463–545.
18. Practice guideline for the treatment of patients with bipolar disorder. In: American Psychiatric Association. American Psychiatric Association practice guidelines for the treatment of psychiatric disorders compendium 2002. Washington (DC): The Association; 2002:547–634.
19. Post RM. New findings on suicide attempts, substance abuse, obesity and more. Curr Psychiatry 2002;1:26–32.
20. 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;62:212–6.
21. 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;60:145–52.
22. Frank E, Swartz HA, Kupfer DJ. Interpersonal and social rhythm therapy: managing the chaos of bipolar disorder. Biol Psychiatry 2000;48:593–604.
23. Miklowitz DJ, George EL, Richards JA, et al. A randomized study of family-focused psychoeducation and pharmacotherapy in the outpatient management of bipolar disorder. Arch Gen Psychiatry 2003;60:904–12.
24. Atack JR. Lithium, phosphatidylinositol signaling, and bipolar disorder. In: Manji HK, Bowden CL, Belmaker RH, editors. Bipolar medications mechanisms of action. 1st ed. Washington (DC): American Psychiatric Press; 2000:1–30.
25. Sadock BJ, Sadock VA. Biological Therapies. Kaplan and Sadock's synopsis of psychiatry: behavioral sciences/clinical psychiatry. 9th ed. Philadelphia: Lippincott, Williams & Wilkins; 2003:974–1150.
26. Keck PE, DelBello MP. Bipolar mania: advances in pharmacologic treatment. Curr Psychiatry 2002;1(Suppl): 6–12.
27. Shelton RC. Treating bipolar depression. Curr Psychiatry 2003;2 Suppl:14–7.
28. Leadbetter R, Messenheimer J, Bentley B, et al. Mood-stabilizing properties of lamotrigine: a review of data from controlled clinical trials. Psychiatr Ann 2002;32:766–72.
29. Ghaemi, SN, Thase ME. Bipolar depression: role of antiepileptics and atypical antipsychotics. Curr Psychiatry 2002;1(Suppl):13–20.
30. Yatham LN. The role of novel antipsychotics in bipolar disorders. J Clin Psychiatry 2002;63 Suppl 3:10–4.
31. Tohen M, Sanger TM, McElroy SL, et al. Olanzapine versus placebo in the treatment of acute mania. Olanzapine HGEH Study Group. Am J Psychiatry 1999;156:702–9.
32. Tohen M, Jacobs TG, Grundy SL, et al. Efficacy of olanzapine in acute bipolar mania: a double-blind, placebo-controlled study. The Olanzapine HGGW Study Group [published erratum Arch Gen Psychiatry 2002;59:91]. Arch Gen Psychiatry 2000;57:841–9.
33. Segal J, Berk M, Brook S. Risperidone compared with both lithium and haloperidol in mania: a double-blind randomized controlled trial. Clin Neuropharmacol 1998;21:176–80.
34. Sachs GS, Grossman F, Ghaemi SN, et al. Combination of a mood stabilizer with risperidone or haloperidol for treatment of acute mania: a double-blind, placebo-controlled comparison of efficacy and safety. Am J Psychiatry 2002;159:1146–54.
35. Keck PE Jr, Versiani M, Potkin S, et al. Ziprasidone in the treatment of acute bipolar mania: a three-week, placebo-controlled, double-blind, randomized trial. Am J Psychiatry 200;160:741–8.
36. Keck PE Jr, Marcus R, Tourkodimitris S, et al. A placebo-controlled, double-blind study of the efficacy and safety of aripiprazole in patients with acute bipolar mania. Am J Psychiatry 2003;160:1651–8.
37. DelBello MP, Schwiers ML, Rosenberg HL, Strakowski SM. A double-blind, randomized, placebo-controlled study of quetiapine as adjunctive treatment for adolescent mania. J Am Acad Child Adolesc Psychiatry 2002; 41:1216–23.
38. Brecher M, Huizar K. Quetiapine monotherapy for acute mania associated with bipolar disorder. The Fifth International Conference on Bipolar Disorder; 2003 Jun 12–14; Pittsburgh, PA [poster].
39. Sachs G, Mullen JA, Devine NA, Sweltzer, DE. Quetiapine versus placebo as adjunct to mood stabilizer for the treatment of acute mania. Bipolar Disord 2002;4(Suppl 1): 133.
40. Regier DA, Farmer ME, Rae DS, et al. Comorbidity of mental disorder with alcohol and other drug abuse. Results for the Epidemiologic Catchment Area (ECA) Study. JAMA 1990;264:2511–8.
41. Levine J, Chengappa KN, Brar JS, et al. Illness characteristics and their association with prescription patterns for bipolar I disorder. Bipolar Disord 2001;3:41–9.
42. McElroy SL, Keck PE Jr. Pharmacologic agents for the treatment of acute bipolar mania. Biol Psychiatry 2000; 48:539–57.
43. Freeman MP, McElroy SL. Clinical picture and etiologic models of mixed states. Psychiatr Clin North Am 1999; 22:535–46, vii.
44. McElroy SL, Keck PE, Pope HG Jr, et al. Clinical and research implications of dysphoric or mixed mania or hypomania. Am J Psychiatry 1992;149:1633–44.
45. Calabrese JR, Rapport DJ, Findling RL, et al. Rapid-cycling bipolar disorder. In: Marneros A, Angst J, editors. Bipolar disorders: 100 years after manic-depressive insanity. Boston: Kluwer Academic Publishers; 2000:89–109.
46. Calabrese JR, Shelton MD, Bowden CL, et al. Bipolar rapid cycling: focus on depression as its hallmark. J Clin Psychiatry 2001;62 Suppl 14:34–41.
47. Kukopulos A, Reginaldi D, Laddomada P, et al. Course of the manic-depressive cycle and changes caused by treatments. Pharmakopsychiatr Neuropsychopharmakol 1980;13:156–67.
48. Calabrese JR, Shelton MD, Rapport DJ, et al. Current research on rapid cycling bipolar disorder and its treatment. J Affect Disord 2001;67:241–55.
49. Geller B, Sun K, Zimmerman B, et al. Complex and rapid-cycling in bipolar children and adolescents: a preliminary study. J Affect Disord 1995;34:259–68.
50. Goodwin GM, Giovanni CB. Maintenance therapy: issues and treatments in long-term management. Curr Psychiatry 2002;1(Suppl):21–7.