Bipolar Disorder for the Primary Care Physician

Case Study and Commentary, Celeste St. John-Larkin, MD, and Michael H. Allen, MD

Abstract

• **Objective:** To review the diagnosis and treatment of bipolar disorder.
• **Methods:** Qualitative assessment of the literature.
• **Results:** Bipolar disorder is a major cause of morbidity and mortality. Due to the incidence and nature of the disorder, it is important to screen any patient presenting with depression for a history of mood swings and manic symptoms. The presence of psychosis or a family history of bipolar disorder can be helpful. First-line treatment for a depressive episode includes lithium or lamotrigine. The addition of an antipsychotic or an antidepressant may be necessary or useful in some cases. Evidence supports avoiding monotherapy with an antidepressant as this is likely to induce mania or rapid cycling. Treatment of severe manic or mixed episodes includes lithium or valproic acid with an atypical antipsychotic. Mild to moderate episodes may be managed with lithium, valproic acid, or an antipsychotic alone. Valproate may be more effective than lithium for some variants. An atypical antipsychotic may be the best choice for management of mild to moderate episodes in primary care settings.
• **Conclusion:** Appropriate diagnosis and treatment of bipolar disorder will help improve outcomes for patients with this potentially devastating but often manageable illness.

Bipolar mood disorder is a major cause of morbidity and mortality. Estimates of lifetime prevalence of bipolar disorder type I range from 0.5% to 1.3% in the United States [1], and as high as 1.5% worldwide [2]. Bipolar disorder type I consists of distinct periods of mania and depression; however, a broad range of symptoms comprise the bipolar spectrum, including hypomania, dysthymia, cyclothymia, and symptoms of elevated mood following antidepressant therapy. Rates of bipolar type I are equal among men and women. Bipolar disorder type II includes episodes of depression and hypomania. Approximately 0.2% to 0.4% of the population is affected, women more commonly than men [1]. The lifetime prevalence of bipolar spectrum disorders has been estimated to be between 2.8% and 6.5% [3].

Onset of bipolar disorder may occur in childhood, adolescence, or early adulthood, with a peak between the ages of 15 and 19 years. In a recent survey, one third of patients reported waiting 10 years between first seeking help and being correctly diagnosed with bipolar disorder [4]. The first episode of mood disturbance is often depression, and patients may first seek treatment with their primary care physicians. Bipolar disorder is associated with impulsive risk-taking behavior, substance abuse, and impaired social and occupational functioning. Substance abuse and divorce rates are at least twice that of the general population. The estimated cost of lost productivity in the United States resulting from bipolar disorder was approximately $15.5 billion in the early 1990s.

**CASE STUDY**

**Initial Presentation**

A 30-year-old man comes to his primary care physician’s office complaining of feeling depressed. He reports that he has been having daily thoughts of wanting to die and has been sleeping poorly. He denies any suicide plans or past attempts. He feels hopeless and guilty about problems with his job and his marriage. He admits to low motivation and increased appetite, with a 20-lb weight gain over the past 6 months. His energy is also decreased, and he has trouble concentrating at his job as a junior high teacher. He denies any previous mental health treatment but has seen a counselor with his wife for several months.

**History**

The patient has been followed by his physician for the past 5 years. He has mild asthma but no other chronic medical problems. The patient is married and has 3 children. He reports that he has been depressed for the past 8 years since a business venture failed. His wife reports that his mood tends to be down for several months each year, especially in the fall and winter. He has had times where he is feeling good, seems to have more energy, and is more productive at work and at home. He currently has a decreased interest in sexual activity, but has had times where he has an increased sex drive. Family history

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**BIPOLAR DISORDER**

**Table 1. DSM-IV-TR Criteria for Depressive Episode**

A. At least 5 of the following symptoms have been present nearly every day during the same 2-week period; at least 1 of the symptoms is either depressed mood or loss of interest or pleasure:

1) Depressed mood most of the day as indicated by either subjective report (eg, feels sad or empty; appears tearful)

2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day

3) Significant weight loss when not dieting, weight gain (eg, a change of more than 5% of body weight in a month), or a change in appetite

4) Insomnia or hypersomnia

5) Psychomotor agitation or retardation (observable by others, not merely subjective feelings of restlessness or being slowed down)

6) Fatigue or loss of energy

7) Feelings of worthlessness or excessive or inappropriate guilt

8) Diminished ability to think or concentrate or indecisiveness

9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or previous suicide attempt or a specific plan for committing suicide


includes the patient’s report that his father has been depressed and had a problem with alcohol, although he has not had any formal treatment. In addition, a cousin on his father’s side had bipolar mood disorder and committed suicide.

**Physical Examination**

On examination, the patient is a mildly overweight male in no acute distress. His general physical examination and vital signs are unremarkable. He is fully oriented and has good eye contact. He has appropriate grooming and hygiene. Psychomotor retardation is noted in his slowed movements. His speech is soft and of normal rate. He appears sad and is tearful when talking about problems with his wife. He feels he is worthless and has no hope of feeling better. He feels life is not worth living at times, but he denies suicidal urges. His thought processes are logical and coherent.

**Initial Treatment**

The patient is begun on a selective serotonin reuptake inhibitor (SSRI) to treat his depressive symptoms and asked to follow-up in 1 month.

- What is the differential diagnosis for a patient first presenting with depression?

Depression may be the first mood episode in more than 50% of patients with bipolar disorder [5]. Thus, it is necessary to consider bipolar mood disorder in the differential diagnosis of any patient presenting with depression. It is important to ask about past episodes of mania or hypomania. Patients often do not recognize these episodes, so asking family members about irritability, periods of decreased sleep, euphoric mood, or increased energy is imperative. The differential diagnosis of depressive symptoms includes major depressive disorder (Table 1), dysthymia, substance-induced mood episode, hypothyroidism, and other medical conditions as well as major depressive episode as part of an underlying bipolar mood disorder.

In a survey of members of the National Depressive and Manic-Depressive Association in 2000, 69% reported that they had been misdiagnosed. The most common misdiagnosis was unipolar depression, but other diagnoses included anxiety, schizophrenia, personality disorder, and alcohol abuse [6]. In one series, 40% of patients consecutively admitted to a hospital with bipolar disorder type I had been previously diagnosed with unipolar major depression [7]. In a study of outpatients with one previous manic or hypomanic episode, 37% had their bipolar depression misdiagnosed as unipolar depression [8].

- What are some clues that a depressive episode is part of a bipolar illness?

A recent review of data on the differences between bipolar and unipolar depression concluded that patients with bipolar depression are more likely to have mood lability, motor retardation, and increased time spent sleeping. They are less likely to have insomnia, weight loss, or psychomotor agitation. Other factors suggestive of bipolar disorder include earlier age of onset, more frequent depressive episodes, and symptoms that begin and end more abruptly. Depressive episodes occurring postpartum in women and those with seasonal variation are more likely to be in the bipolar spectrum [9]. In comparison to patients with unipolar depression, bipolar patients are more likely to have an earlier age of onset, more total mood episodes, and hyperactive traits as children [10]. Patients with bipolar depression are more likely to have psychotic symptoms and more frequent and significant suicide attempts [11].

Family history is another important aspect of diagnosis. Twin and epidemiologic studies provide evidence that bipolar mood disorder is highly heritable, although the genetic basis is poorly understood [12]. First-degree relatives of bipolar probands have a 20% lifetime risk of developing bipolar disorder. In a national survey of patients with bipolar
disorder, a family history of bipolar disorder predicted an earlier age of onset of symptoms and a more difficult course of illness [4].

- What is the differential diagnosis for a patient with mood and psychotic symptoms?

Approximately 58% of patients with bipolar mood disorder have a lifetime history of at least 1 psychotic symptom. Psychosis occurs in both phases of bipolar illness but is more common in mania. Grandiose, paranoid, and persecutory delusions are more common than hallucinations [11]. A differential diagnosis in the patient with mood and psychotic symptoms includes schizophrenia, schizoaffective disorder, delusional disorder, and brief psychotic disorder. Psychosis may be the presenting symptom in some patients with bipolar disorder. Additional history may suggest that the patient is depressed or has evidence of mania, such as grandiosity or decreased need for sleep. A family history of bipolar mood disorder weighs in favor of patients having a mood disorder underlying their psychosis [13]. With psychosis related to a mood disorder, the psychotic symptoms resolve as the mood episode improves. There are no psychotic symptoms between episodes.

- How is the diagnosis of bipolar disorder confirmed?

The diagnosis of bipolar disorder is clinical. There are no laboratory tests or imaging studies that confirm the diagnosis. Medical or neurologic causes that can contribute to mood symptoms include thyroid problems, steroid use, and substance abuse (eg, methamphetamine). Laboratory testing should initially include measurement of thyroid-stimulating hormone and glucometry. Pulse oximetry may be helpful if the patient appears agitated. Baseline chemistry, complete blood count, and liver function panel are necessary for initiation of several drugs used in treatment of bipolar mood disorder.

- What are the first steps in treatment of bipolar depression?

**Management of Bipolar Depression**

The first step in management of the bipolar patient is to ensure the safety of the patient and others. Suicidal ideation occurs in 14% to 59% of bipolar patients and the suicide rate is at least 7% and perhaps as high as 19% [11]. Suicide is most likely during depressed and mixed episodes. A 38-year follow-up study of hospitalized depressed patients found that patients under long-term medication treatment had a significant reduction in overall mortality and a 2.5-fold lower suicide rate than untreated patients. Rates of suicide in this population were 8% in bipolar I patients and 9% in bipolar II patients [14]. Other studies have suggested that patients with bipolar II are at higher risk for completing suicide [15]. Factors associated with increased suicide risk include early age at onset of illness, history of hospitalization with depressive episodes, drug abuse, and family history of mood disorders [16]. Patients with suicidal ideation should be assessed for inpatient treatment.

**Medications**

First-line medications typically used to treat bipolar disorder include lithium, several anticonvulsants, and atypical or second-generation antipsychotics. Evidence for the use of these medications depends on the phase and severity of the illness. In addition to the American Psychiatric Association treatment guidelines [13], the International Consensus Group on Bipolar I Depression recently published treatment guidelines specific to bipolar depression [17]. Clinicians should address treatment of the entire illness, not just the acute manic or depressive episode.

First-line therapy for bipolar depression includes lithium or lamotrigine. Lithium has been superior to placebo in multiple studies [17–20]. In one literature review, 8 out of 9 controlled studies found that lithium was superior to placebo in bipolar depressed patients [21]. Clinical trials have also evaluated lithium versus combination therapy with lithium and an antidepressant. A recent study investigated the efficacy of lithium alone compared with lithium plus either imipramine or paroxetine. Adding an antidepressant to lithium conferred no significant advantage for patients treated with lithium at levels above 0.08 mEq/L. Patients with lower lithium levels (< 0.08 mEq/L) did better on imipramine and paroxetine [22].

Lamotrigine has been shown to be more effective than placebo in a double-blind, placebo-controlled trial in the treatment of acute bipolar I depression [23]. Daily doses of 200 mg were effective on more outcome measures than 50-mg doses. The therapy was well tolerated, with only headache occurring more often in the lamotrigine groups versus placebo. The most concerning adverse event with lamotrigine is Stevens-Johnson syndrome. Risk of rash with lamotrigine is greatly decreased by a slow titration with daily doses of 25 mg for 2 weeks, then 50 mg for 2 weeks, followed by 100 mg for 1 week, with titration upward as needed.

There is inadequate evidence regarding the treatment of bipolar depression with antidepressants [24]. Bipolar patients are generally excluded from antidepressant trials as...
antidepressants can potentially induce mania or rapid cycling. Monotherapy with an antidepressant should be avoided. In one study of hospitalized patients, 25% switched from depression to mania or hypomania with the use of an antidepressant. Tricyclic antidepressants were most likely to induce switching, and the risk was significantly reduced with the addition of a mood stabilizer [25]. A recent randomized controlled trial of mood stabilizers with an SSRI versus placebo plus SSRI indicates that SSRIs alone are less effective for bipolar depression than an SSRI plus a mood stabilizer. SSRIs alone are also less likely to prevent depression in the maintenance phase [26]. One small study in bipolar depressed patients found equal acute efficacy for both bupropion and desipramine when added to lithium or an anticonvulsant. However, in 1 year of follow-up, patients taking desipramine were more likely to experience mania/hypomania than patients on bupropion [27]. There are no studies comparing bupropion with SSRIs.

Atypical antipsychotics are indicated for the treatment of mania and may also have a role in treating bipolar depression. A recent trial in which patients received olanzapine, the combination of olanzapine and fluoxetine, or placebo found that both active treatments were superior to placebo in treatment of depressive symptoms [28]. Neither group had higher rates of mania than placebo. Quetiapine at a dose of 300 mg/day has also demonstrated superiority to placebo for a range of depressive symptoms. Patients with depression with psychotic features should receive an antipsychotic, although nonpsychotic depressed patients may also benefit.

For patients who do not respond to the initial mood stabilizer, the next step is to ensure an optimal dose by measuring the serum level or attempting to increase the dose. After optimizing the dose of the initial medication, consider adding lamotrigine, bupropion, or an SSRI.

ECT
Electroconvulsive therapy (ECT) is an option for patients who do not respond to or do not tolerate medications. Many patients who have had ECT find it so effective that they request ECT for their subsequent depressive episodes. Five out of 7 clinical trials found ECT more efficacious than antidepressants in treating bipolar depression including depression with psychotic features [21]. ECT is also safe for depression during pregnancy, where medications may pose a risk to the fetus.

Follow-up Visit
The patient misses his follow-up appointment and returns to the clinic 2 months later with his wife. He reports sleeping 3 to 4 hours per night and waking up with lots of energy at 4 AM every day. He then cleans the house repetitively and makes lunches for the family. In the afternoon, his energy may flag, but he will feel fully rested after a 20-minute nap. His wife reports that he has been talking much more than usual. He has trouble focusing and jumps from topic to topic. He is easily angered and recently lost his job after he got into an argument with his boss. His sexual drive is increased. He has plans to take the family on an expensive vacation and talks about starting a new digital photography business. He admits to hearing music that is not there and describes seeing things in very vivid colors. His family reports that his mood may change rapidly from irritable to exuberant. The patient’s wife admits that he has had some periods of increased energy and decreased need for sleep in the past, but she has never seen him like this.

The patient’s general physical examination is unremarkable. On mental status examination, he has good eye contact but significant psychomotor agitation, as evidenced by frequent standing and pacing during the interview. He is appropriately dressed, but his hair is disheveled. He is carrying a pile of books, papers, and photographs and repeatedly uses them to demonstrate his ideas. He is alert and oriented. He states his mood is “great.” His affect is euphoric, inappropriately bright for the situation. He is impatient at times with his wife and the interviewer. His thought processes are tangential and he displays flight of ideas, jumping from talking about his job to his kids to religion to his plans for all the money from his new business. He denies any morbid or suicidal thoughts.

• What is the differential diagnosis for this patient at his follow-up visit?

The patient most likely has developed mania following the use of an antidepressant (Table 2). He may have had an underlying bipolar disorder, given his wife’s report of past episodes of elevated mood and energy. If a patient has no history of prior manic or hypomanic episodes but clearly has an episode after use of an antidepressant, he can be diagnosed with bipolar mood disorder not otherwise specified. The primary difference between mania and hypomania is that hypomania lasts only 4 days and causes less dysfunction. This patient’s occupational and marital dysfunction qualifies him for a diagnosis of mania.

• What does a mixed episode look like?

Patients with bipolar mood disorder may present with mixed states. These patients often complain of feeling depressed most of the day, but will have periods of increased energy,
Management of Acute Mania and Mixed States

The first step of treatment is to discontinue antidepressants if they are present and begin mood stabilizing medication. If the patient is already on a mood stabilizer, begin by optimizing the dose of that medication as above. Severe manic or mixed episodes are treated with lithium or valproate plus an atypical antipsychotic. In patients who are not as severe, treatment begins with monotherapy with lithium, valproate, or an atypical antipsychotic alone. Alternative mood stabilizers include carbamazepine, oxcarbazepine, and lamotrigine. The dose of a single agent should be optimized, and if still unsuccessful in controlling symptoms, addition of a second agent or an atypical antipsychotic may be necessary. Short-term use benzodiazepines is recommended in treatment of severely ill or agitated patients [13].

Lithium has the strongest evidence base for the treatment of manic episodes and has been the mainstay of treatment for bipolar disorder for over 40 years. Five studies have demonstrated that lithium is superior to placebo [29–34]. Lithium has been shown to be as effective as valproic acid, carbamazepine, and typical and atypical antipsychotics in clinical comparator trials [34–43]. Additional studies indicate that lithium is less effective in mixed states than other mood stabilizers [44–48]. A good response to lithium is predicted by euphoric mania, lack of rapid cycling, absence of substance abuse, a positive family history of bipolar mood disorder, and less than 10 lifetime episodes of mania or depression [49].

Valproic acid (divalproex, sodium valproate) is also supported by good evidence in the treatment of mania. In 4 randomized, placebo-controlled studies, it has shown superior efficacy to placebo, with response rates of approximately 50% [34,48,50,51]. Divalproex has demonstrated efficacy comparable with haloperidol and olanzapine in reduction of mania and psychosis [52,53]. Randomized trials have also suggested that divalproex is more efficacious than lithium in mixed states, dysphoric mania, and in patients with multiple prior mood episodes. In the largest of the randomized controlled trials, divalproex was found to be equally effective in patients with rapid-cycling bipolar disorder [34].

Evidence for carbamazepine is not as strong; however, it has been shown to be superior to placebo in 1 randomized trial [54], comparable to lithium in 2 trials [35,36], and comparable to chlorpromazine in 1 randomized trial [55]. Pooled data from controlled studies suggest a response rate of 50% for carbamazepine, 56% for lithium, and 62% for valproate [56]. However, carbamazepine induces the hepatic enzyme cytochrome P-450, leading to decreased drug levels of valproate, oral contraceptives, many antidepressants, and antipsychotic medications. Carbamazepine also induces its own.
metabolism via this mechanism [13]. Oxcarbazepine, an analog of carbamazepine, may have fewer side effects and does not induce its own metabolism. Oxcarbazepine was more effective than placebo in 1 controlled trial [50]. The most common side effect is hyponatremia.

With the success of divalproex and carbamazepine, attention has focused on other anticonvulsants with mixed results. One double-blind, randomized, placebo-controlled crossover study found that lamotrigine monotherapy was superior to both gabapentin and placebo in patients with mania and depression. Gabapentin did not separate from placebo [57]. One small randomized trial found that lamotrigine was as effective as lithium in treating acutely manic hospitalized patients. In this study, lithium levels were slightly lower than the usual therapeutic dose [58]. Topiramate, tiagabine, and zonisamide have been studied in open-label trials, but further study is needed before they can be recommended for routine use [59]. Topiramate may be helpful as an adjunct in patients who also need assistance with weight loss, as this is a common side effect of topiramate.

Antipsychotics are generally effective in acute mania. The second-generation antipsychotics, with their lower side-effect burden, are now recommended as monotherapy in mild cases or as adjuncts in more severe cases. Olanzapine is the best studied, with 4 controlled trials demonstrating equivalence [52] or superiority [60] to divalproex and superiority to placebo in acute mania [61,62].

Risperidone has also proven effective in treatment of acute mania. Three double-blind, placebo-controlled trials of risperidone as monotherapy demonstrated significantly improved manic symptoms in patients with or without psychosis [63–65]. Quetiapine was effective in 2 double-blind placebo-controlled trials. In these trials, quetiapine at doses averaging 598 mg were superior to placebo and as effective as lithium and haloperidol [66]. Ziprasidone and aripiprazole also have placebo-controlled trials indicating efficacy in acute mania as monotherapy, although with lower effect sizes [67,68].

Given the severity of the behavioral symptoms in acute mania, combinations are often used to accelerate improvement. The atypical antipsychotics in combination with lithium or an anticonvulsant are particularly effective. In a randomized placebo-controlled trial of patients with acute mania who had not responded to either lithium or valproate alone for 2 weeks, olanzapine was more effective than placebo as an adjunctive treatment. In addition, olanzapine plus a mood stabilizer was superior to placebo in treating depressive symptoms associated with mania [69]. Two randomized controlled trials of risperidone versus placebo in patients taking lithium or valproate showed significant reduction in manic symptoms with risperidone [70,71]. In a prospective study of the same combination, risperidone also significantly decreased patient’s depressive symptoms [72]. Quetiapine has also been found to be superior to placebo in combination with lithium or divalproex [73].

See Table 4 for dosing information.

- How does treatment of rapid-cycling bipolar disorder differ?

Rapid cycling refers to patients with 4 or more episodes of major depression, mania, mixed episodes, or hypomania per year, according to the DSM-IV. Research has suggested that there is a spectrum of rapid-cycling bipolar disorder. Rapid-cycling patients generally have lower response rates to most treatments [74]. A recent study suggests that patients with rapid-cycling bipolar disorder have underlying dysfunction of the hypothalamic-pituitary-thyroid axis [75]. Therefore, it is important to treat any medical or comorbid conditions that could make cycling worse, such as hypothyroidism and substance use. Antidepressants may make cycling worse and should be tapered and discontinued if possible.

Initial treatment should be with lithium, valproate, or lamotrigine. A double-blind, placebo-controlled study of lamotrigine as prophylaxis in rapid-cycling outpatients demonstrated superiority of lamotrigine, especially in bipolar II patients [76]. The International Consensus Group on Bipolar I Depression guidelines noted that depression is often the more prominent symptom in rapid-cycling bipolar disorder. When patients with rapid-cycling bipolar disorder are not responding to treatment, the guidelines suggest combining 2 first-line agents [17]. Antidepressants are only considered when multiple other treatments have failed, such as in patients already taking 2 or 3 first-line agents. One controlled, double-blind study of olanzapine versus placebo found a reduction in manic but not depressive symptoms [77]. Data on other atypical antipsychotics are limited.

Additional Follow-up

Given his manic symptoms, the patient’s antidepressant is discontinued. With the severity of his symptoms and history suggesting prior episodes, mood stabilizing medication is indicated. A number of options are presented, including beginning treatment with lithium, divalproex, or an atypical antipsychotic. The patient chooses lithium because he knew of a friend with bipolar disorder who took the medication. His wife is very concerned about his irritability and poor sleep. In hopes of decreasing these symptoms as rapidly as possible, quetiapine is added at an initial dose of 100 mg twice a day.

The patient has gradual resolution of his manic symptoms. He continues medication to prevent the recurrence of
a depressive or manic episode. He and his wife are referred back to his counselor for family therapy. He begins attending a bipolar support group through his local chapter of the National Alliance for the Mentally Ill.

How does treatment differ during periods of remission?

Maintenance Therapy

The goals of maintenance therapy include preventing relapse, decreasing the frequency of cycling, and improving functioning. Determining which patients need prophylactic treatment is based on clinical judgment. At a minimum, patients with 2 or more previous mood episodes should be placed on prophylactic medication. Maintenance therapy is indicated after only 1 episode if mania was severe or included psychotic features. Other factors that suggest keeping patients on maintenance therapy include family history, sudden onset of mood symptoms, high suicide risk, and onset in adolescence or after age 30 years. The duration of maintenance therapy depends on the number and severity of past mood episodes and the length of time between episodes [11]. Subsyndromal symptoms often herald relapse; therefore, prophylactic medication should be continued as long as any symptoms are present. Lithium and valproate have the best evidence for maintenance treatment. Alternatives include lamotrigine, carbamazepine, oxcarbazepine, or atypical antipsychotics [13].

Multiple studies have demonstrated the efficacy of lithium as maintenance therapy. However, a meta-analysis of 5 randomized-controlled trials of lithium maintenance with a total of 770 patients found that 1 patient would avoid relapse for every 5 patients treated for 1 to 2 years with lithium. One mania was prevented for every 10 patients and 1 depression for every 14 patients [78]. There has been one placebo-controlled, randomized trial of divalproex versus lithium. The 12-month study found no significant difference in time to development of any mood episode; however, patients on divalproex were significantly less likely to discontinue the study because of a recurrent mood episode. Divalproex also tended to be better at controlling subsyndromal depressive symptoms [79]. Recently, a placebo-controlled 18-month-long trial of lithium and lamotrigine in patients who had recently been manic or hypomanic found that both were superior to placebo for preventing the occurrence of another mood episode. Lithium was more effective in preventing mania, while lamotrigine was more effective in preventing depression [80]. The effectiveness of carbamazepine and other anticonvulsants for prophylaxis is unclear.

Olanzapine has demonstrated efficacy as maintenance monotherapy, and other atypical antipsychotics may be useful. A 47-week double-blind trial of olanzapine versus divalproex found no statistical significance in time to recurrence of an affective episode or rates of relapse into mania or depression [81]. If an atypical antipsychotic was used with a mood stabilizer during an acute episode, an attempt may be made to reduce the dose or discontinue the antipsychotic during maintenance therapy. However, continuing treatment

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with an antipsychotic may be necessary for patients prone to psychosis or frequent relapses, irritability, or impulsivity. Also, some patients may prefer the side effect profile of antipsychotics. Tardive dyskinesia is much less frequent with the newer antipsychotics, but patients should still be monitored for the development of abnormal involuntary movements.

- Is psychotherapy helpful in bipolar disorder?

**Psychosocial Treatments**

At their best, pharmacologic treatments may be only partially effective and do not address many aspects of the disease process. For example, regular sleep habits and stable interpersonal relationships are particularly important for bipolar patients. Education and psychotherapy are valuable adjuncts to pharmacotherapy. Several types of psychotherapy have been developed to target the different aspects of the disorder. The focus of therapy varies with the stage of the illness. In the acute phase, the focus is on assessment, support, and reassurance. Traditional psychotherapy is not effective during an acute manic episode, as reality testing and judgment are usually impaired. In the stabilization phase following an acute episode, therapy is structured and task-oriented (eg, helping ensure medication adherence). During the maintenance phase, therapy focuses on helping the patient gain insight regarding their illness, with attention to communication and problem-solving skills [82].

Family-focused therapy (FFT) is a 9-month program of psychoeducation and skills training. One randomized controlled trial compared FFT plus pharmacotherapy with pharmacotherapy and crisis management. Patients in the FFT group had 35% fewer relapses and went an average of 5 months longer without relapse than patients in the control group [83]. A randomized controlled trial of patients in remission found that a structured psychoeducation group therapy significantly reduced the recurrence of manic, depressed, and mixed episodes, increased the time to recurrence, and decreased the number of hospitalizations at 12-month follow-up [84]. Interpersonal and social rhythm therapy incorporates a self-monitoring program to help patients with bipolar disorder maintain a regular schedule, which has been helpful in decreasing mood lability [85]. Cognitive behavioral therapy is helpful in combination with mood stabilizers in preventing relapse of mania or depression [86] and in treatment of bipolar depression, without use of antidepressants [87].

Patients with bipolar mood disorder are likely to have other psychiatric comorbidities, which have implications for treatment of both disorders. A survey of 288 outpatients with bipolar I and II found that 65% had at least 1 lifetime comorbid psychiatric disorder, and 33% had a current comorbid disorder. Comorbidities are associated with an earlier age of onset of the mood disorder, more severe episodes, rapid cycling, family history of substance abuse, and limited occupational functioning. Anxiety and substance use disorders are the most common comorbidities. Eating disorders, most often bulimia, were the third most common. Panic disorder and social phobia were the most common anxiety disorders [88]. Although antidepressants are usually used to treat anxiety disorders, they may create a more difficult course for bipolar patients and should be used with caution.

Attention-deficit/hyperactivity disorder (ADHD) is also frequently comorbid with bipolar disorder. Symptoms such as increased motor activity, talkativeness, and distractibility may occur in both disorders [89]. A prospective 4-year follow-up study of children with ADHD found that they had an increased risk of developing bipolar mood disorder, independent of the overlapping symptoms [90]. In a study of 51 adults referred to clinical trials for treatment of ADHD, 24 patients also met criteria for bipolar mood disorder. The majority of these patients (88%) had bipolar II [91]. Stimulants used to treat ADHD symptoms theoretically exacerbate mania or psychosis in patients with bipolar mood disorder. One retrospective study in adolescents suggested that patients with a history of stimulant treatment had a younger age at onset of bipolar disorder, independent of the presence of ADHD [92]. Because of this potential risk, an open-label trial of bupropion in adults with ADHD and bipolar mood disorder was recently completed. There was significant improvement in ADHD and depressive and manic symptoms. One patient developed hypomania and dropped out of the study [93]. While this is preliminary data, it suggests an alternative to stimulant use in patients with comorbid bipolar disorder.

It is important to address substance abuse in bipolar patients, as multiple studies have shown that alcohol and other drugs worsen the course of the illness. Substance users are 4 times more likely to have onset of mood symptoms before age 20 years. Significant problems exacerbated by substance use include more frequent episodes, more mixed episodes, increased comorbidity, slower time to recovery, and more lifetime hospitalizations [94,95]. A long-term follow-up study of 50 new-onset bipolar patients found that duration of alcohol abuse was associated with length of time spent in depression, while cannabis abuse was associated with manic symptom duration [96]. Bipolar patients should be encouraged to abstain and may require treatment for the substance use disorder in order to stabilize their mood.
addition to direct effects on mood and behavior, substance use has a deleterious effect on compliance.

Patients with bipolar disorder are often nonadherent with medication regimens. Bipolar patients are more often aware of depression than mania and are particularly susceptible to nonadherence when they feel "well," which may mean manic. It is important to remind these patients about the long-term consequences of mania on their interpersonal relationships and occupational functioning. Factors influencing a patient’s medication adherence include tolerability and simplicity of the medication regimen and the patient’s perception that the physician is knowledgeable and caring. Patients are often reluctant to tell their physician they have not been taking their medications correctly. Inquiring in a manner that suggests the physician is prepared for partial adherence may help the patient to be more open, eg, “How many doses did you miss in the past week?” Enlisting the help of family members is important. Blood levels should be monitored in patients taking medications such as valproic acid, lithium, and carbamazepine.

- When should patients be referred to a psychiatrist?

Referrals for specialist evaluation may be driven by questions about diagnosis, complications, or poor response. Suicidal ideation, serious behavior problems, or inability to meet role expectations may warrant specialty assessment and possibly hospitalization. Comorbidity (eg, with anxiety disorders) may pose pharmacologic conflicts. Poor response to initial medications, as a result of side effects, treatment failure or poor compliance may suggest the need for consultation.

CONCLUSION

Patients with bipolar disorder frequently present to primary care physicians, and primary care physicians are increasingly required to deal with mania, depression, and maintenance. Due to the incidence and nature of the disorder, it is important to screen any patient presenting with depression for a history of mood swings and manic symptoms. The presence of psychosis or a family history of bipolar disorder can be especially helpful. First-line treatment for a depressive episode includes lithium or lamotrigine. The addition of an antipsychotic or an antidepressant may be necessary or useful in some cases. Evidence supports avoiding monotherapy with an antidepressant, as this is likely to induce mania or rapid cycling.

Treatment of severe manic or mixed episodes includes lithium or valproic acid with an atypical antipsychotic. Mild to moderate episodes may be managed with lithium, valproic acid, or an antipsychotic alone. Valproate may be more effective than lithium for some variants. An atypical antipsychotic may be the best choice for management of mild to moderate episodes in primary care settings. Awareness of common comorbidities that complicate diagnosis and treatment and adjunctive psychosocial treatments will help improve outcomes for patients with this potentially devastating, but often manageable illness.

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References

BIPOLAR DISORDER


