With the recent awareness of the bipolar spectrum, the interest and concern of physicians regarding the depressive side of bipolar disorder has emerged. Depression is the modal phase of bipolar disorder, as well as the phase that imparts the greatest risk for suicide. Despite these realities, little is known about the management of bipolar depression and much of what is known is complicated by conflicting reports regarding the use of antidepressants as either short- or long-term treatment modalities. This fear among physicians of complicating a patient’s course secondary to antidepressant use combined with the fact that presently available mood stabilizers are less than reliable antidepressants has resulted in far more questions about management than answers. This article explores the clinical issues involving the depressive states, reviews some of the emerging data, and, it is hoped, lends some guidance regarding treatment options.

Bipolar disorder is often defined simply as a cyclic or phasic mood disorder characterized by intermittent episodes of depression and mania. Unfortunately, this definition does not always accurately or completely describe this complex mental disease state, as bipolar disorder is now considered to be a spectrum of illnesses. Further, phases of this illness are not limited to depression and mania, but are also include mixed states, rapid cycling, and hypomania, as well as persisting subsyndromal symptoms of depression and mania.1

These expanded concepts of bipolar disorder, an illness that is estimated to affect 2.3 million adults in the United States, have led to a reassessment of its lifetime prevalence rate, currently estimated at 3.7%.1,2 Despite this emerging information, many physicians believe the idea of failing to recognize a patient having this illness to be counterintuitive. How could a physician miss noticing the symptoms of bipolar disorder in a patient currently having an episode of mania or hypomania? Yet, bipolar disorder in most affected patients is initially misdiagnosed, the most common misdiagnosis being unipolar major depression.3 These data, supported by similar results from other studies, support the notion that physicians face a great challenge in recognizing patients with bipolar disorder.4,6

This monumental failure at recognizing patients with bipolar disorder is attributable to a number of factors. Although physicians are trained to evaluate patients for evidence of episodes of mania or hypomania, patients frequently do not perceive these episodes as illness and therefore deny the symptoms on questioning. Additionally, patients may fail to endorse symptoms on screening instruments or fail to seek care during episodes. A second factor is that in patients with bipolar disorder, initial as well as early subsequent episodes of mood change are more commonly depressive episodes, rather than manic or hypomanic episodes. This factor may lead physicians to assume a diagnosis of unipolar depression.

Primary care physicians have been trained to believe that the prevalence of bipolar disorder is rare, particularly in outpatient settings, compared with the prevalence of unipolar disorder. In fact, bipolar disorder is common, affecting an estimated 30% of patients with depression seen in primary care settings.8 The modal phase of bipolar disorder is depression. It is this phase, most closely associated with social and occupational dysfunction, as well as an increased risk of suicidal thinking and behavior, that may prompt a patient to seek treatment. Finally, a diagnosis of bipolar disorder may be delayed or masked by complications from other psychiatric comorbidities, particularly substance abuse, anxiety disorders, and migraine syndromes.

As experts continue to explore the vicissitudes of bipolar disorder to refine definitions of the bipolar spectrum, one fact is clear: Depression, with its abundant medical, social, and occupational consequences, is the phase of bipolar disorder that most often confronts primary care physicians in outpatient practice. Consequently, physicians treating patients with that phase must exert efforts toward sensitivity to the recognition of bipolar depression, as well as focused strategies for its acute and long-term management.

Recognizing Patients With Bipolar Depression

The depressive phases of bipolar disorder predominate the disease’s course, in initial episodes, as well as in relapse.
Therefore, it is challenging to make an early and accurate diagnosis of the disorder. Early recognition and management of bipolar disorder may arrest the long-term progressive tendency of the illness. This arrested progression, in turn, can prevent the emergence of substance abuse problems, rapid cycling, and resistance to pharmacologic treatment, as well as negative consequences associated with social and occupational dysfunction.

Although early diagnosis of bipolar disorder can be difficult for even the most experienced physicians, there are diagnostic clues that primary care physicians can incorporate into their clinical assessments to raise sensitivity to the disorder. The first, and most important, step is to consider bipolar disorder within the differential diagnosis when assessing a patient with complaints of mood change (Figure 1). As physicians remember that unipolar depression is a diagnosis of exclusion, their recognition of bipolar depression, as well as mood disorders secondary to medical conditions and substance use disorders, will improve.9

During patient evaluations, physicians should consider clinical features suggestive of bipolar depression, the most important of which may make up the points of what may be referred to as the bipolar diagnostic star (Figure 2).10,11 Among these features is early age of onset, as evidence suggests that most patients with bipolar disorder have onset of illness before 20 years of age.12 (Patients with unipolar disorder tend to have a later average age of onset.) The earlier the onset of mood symptoms, the greater the likelihood of a diagnosis of bipolar disorder versus unipolar disorder. Another consideration is family history of mental illness, and, more specifically, family history of bipolar disorder. The disease appears to be an autosomal-dominant disorder with incomplete penetrance, and a 70% concordance rate in monozygotic twins.13

Physicians should note the presenting symptoms, as well as the course of the symptoms. They should screen all patients with depression for manic and hypomanic symptoms, and question patients' history of episodes. Symptoms of mania can co-occur with depressive symptoms, a phase of bipolar disorder known as “mixed state.” Unfortunately, bipolar disorder, mixed state is frequently misdiagnosed as agitated depression. Physicians should consider the diagnosis of bipolar disorder, mixed state when a patient has predominating symptoms of agitation, irritability, anxiety, and insomnia that occur against a background of depressive symptoms.

Other presenting or classic symptoms suggestive of bipolar disorder include hypersomnia, psychomotor retardation, abrupt onset, termination of episodes (eg, “mood swings,” postpartum episodes of depression), and the presence of comorbidities (eg, substance abuse, anxiety disorders, attention-deficit hyperactivity disorder [ADHD]).10

The final consideration is patients' prior response to treatment. The antidepressant refractory depression rate is reported to be as high as between 30% and 40%.14 Part of the explanation for this astonishing treatment failure rate can be attributed to a lack of diagnostic precision. Antidepressant failure or adverse reactions while patients are on antidepressant therapy can be important clues leading to a diagnosis of bipolar disorder, as patients with bipolar disorder generally do poorly on antidepressant monotherapy. In fact, tricyclic antidepressant agents have long been associated with induction of mania, hypomania, and cycle acceleration when used alone as treatment.15

It appears from other data, however, that selective serotonin reuptake inhibitors (SSRIs) and bupropion hydrochloride impart much less risk.16 Nonetheless, antidepressant monotherapy, regardless of the agent chosen, is contraindicated in patients with bipolar depression. The use of a safer antidepressant (eg, SSRIs, bupropion hydrochloride) in combination with a mood stabilizer, however, can be highly effective. This efficacy is evidenced by the recent US Food and Drug Administration (FDA) approval of the olanzapine-fluoxetine hydrochloride combination for the treatment of patients with acute bipolar depression.17

In addition to the five points of the bipolar disorder diagnostic star, physicians should consider other features in the evaluation of patients with depression. Given the seriousness of the symp-
Lithium

The small number of studies of lithium as treatment for patients with acute bipolar depression are considered flawed. Yet, lithium remains the most widely used first-line treatment for patients with this disorder. The studies of lithium include a pooled analysis of existing studies in which lithium’s effectiveness was estimated to be a disappointing 36%. Additionally, several predictors of lithium nonresponse have been reported, including the presence of bipolar disorder, mixed state, a rapid cycling course (four or more episodes per year), and comorbid substance abuse. Given the frequency of these features in patients with bipolar disorder and considering the difficulties inherent in using lithium, it is often an unwise first choice.

Lithium, however, has been systematically investigated as maintenance treatment for patients with bipolar disorder, including two 18-month, placebo-controlled studies versus lamotrigine. Most available data support lithium’s ability to prevent both manic and depressive relapse, though the drug is clearly more effective at preventing mania than depression. In fact, in two comparison studies with lamotrigine, lithium prolonged time to manic relapse but was no better than placebo at prolonging time to depressive relapse.

With respect to safety and tolerability issues, lithium has a black box warning for a narrow therapeutic index, making routine serum monitoring essential. Lithium is pregnancy category D, and it is commonly associated with weight gain, tremor, acne, hypothyroidism, and renal impairment.

Anticonvulsants

Much of the interest in the use of anticonvulsants for the treatment of patients with bipolar disorder grew out of reports regarding the efficacy of carbamazepine in the treatment of patients with acute mania. A controlled-release formulation of the drug may, in fact, eventually receive an indication for acute mania. Unfortunately, researchers have not initiated large systematic investigations of carbamazepine as treatment for patients with depression associated with bipolar disorder or for maintenance. The limited...
data available reveal only modest acute antidepressant effects associated with carbamazepine in monotherapy. In a study by Griel et al that compares the maintenance effect of carbamazepine with lithium for 30 months, lithium had a statistically significant advantage. Overall, carbamazepine appears to have limited utility in the management of patients with bipolar disorder.

Since receiving registration for the treatment of patients with acute mania in 1995, divalproex has become the most widely prescribed mood stabilizer in the United States. Interestingly, divalproex has not been investigated in large placebo-controlled trials of patients with depression. Further, the results of one small pilot study by Sachs et al failed to statistically separate divalproex from placebo, and the results of open-label trials with the drug reveal only modest antidepressant effects. Bowden et al conducted a large placebo-controlled study of divalproex versus lithium as maintenance treatment for patients with bipolar disorder. Results indicate a failed trial for both active treatment modalities. Despite lackluster results as treatment or maintenance in patients with acute depression, the consensus among experts is that divalproex possesses at least modest antidepressant effects in both acute depression and maintenance treatment.

Tolerability and safety issues with divalproex include three black box warnings, including risks of neural tube defects in pregnant women. The drug is more commonly associated with weight gain, gastrointestinal disturbances, and hair loss.

Lamotrigine is a novel anticonvulsant that recently received FDA approval for maintenance treatment of patients with bipolar disorder, based on the strength of two 18-month placebo-controlled trials of lamotrigine versus lithium. In both studies, lithium was more effective than lamotrigine at preventing manic relapse; however, lamotrigine was superior to lithium at preventing depressive relapse. Additionally, lamotrigine has been studied in patients with acute bipolar depression in two large placebo-controlled trials. The results of both trials demonstrated statistically significant separation over placebo on the Montgomery-Asberg Depression Rating Scale. Lamotrigine clearly possesses antidepressant efficacy. Failed trials in acute mania, however, as well as the drug’s failure to prevent manic relapse in maintenance studies, indicate that lamotrigine cannot be considered a bidirectional mood stabilizer. Ultimately, lamotrigine may become more important in the long-term management of patients with bipolar II disorder, in which depression is a more serious threat than hypomania. The drug may also serve as an adjunct treatment for maintenance in patients with bipolar I disorder.

Lamotrigine carries a black box warning for life-threatening rash, which necessitates a gradual titration of the drug to therapeutic doses to limit this risk. This slow titration severely limits the agent’s potential use in patients who are acutely depressed. In addition to the risk of rash, lamotrigine has been associated with headache, nausea, and dizziness. Other anticonvulsants, such as gabapentin and topiramate, have not demonstrated significant utility as monotherapy in controlled trials in patients with bipolar disorder. Interest continues, however, in the usefulness of topiramate as an adjunct treatment for the disorder.

Oxcarbazepine, a congener of carbamazepine, has generated interest because of its superior tolerability profile over carbamazepine. Unfortunately, no large systematic investigations into the drug’s usefulness in patients with bipolar disorder have been conducted.

Antipsychotics

Drugs from the antipsychotic classes are often overlooked in discussions regarding mood stabilizers. It is important to note, however, that chlorpromazine was the first FDA-approved treatment for patients with acute mania and that all conventional antipsychotics have demonstrated efficacy in this phase of bipolar disorder. Conventional antipsychotic agents have not been found to be useful as antidepressants, however, and have been found to frequently exert a depressogenic effect. Therefore, all conventional antipsychotics can be considered antimanic agents, but not bidirectional mood stabilizers.

Atypical antipsychotic agents, however, appear to hold more promise as true mood stabilizers. During the mid-1970s, the first atypical antipsychotic, clozapine, was reported to exert bidirectional effects on mood. Since that time, numerous reports of clozapine’s useful-

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**Table**

Reported Disruption in Work, Social Life, and Family Life: Respondents With Bipolar Disorder and Depression Versus Respondents With Unipolar Disorder and Depression (n = 794)*

<table>
<thead>
<tr>
<th>Group</th>
<th>Marked or Extreme Disruption 4 Weeks Before Survey†</th>
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<tbody>
<tr>
<td></td>
<td>Work, %‡</td>
</tr>
<tr>
<td>Respondents with bipolar disorder§</td>
<td>30.1</td>
</tr>
<tr>
<td>Respondents with unipolar disorder¶ ¤</td>
<td>13.3</td>
</tr>
<tr>
<td>Control subjects</td>
<td>1.1</td>
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</tbody>
</table>


†P < .001 among groups for each dimension.

‡$P < .05.

§Subjects were considered “bipolar depressed” if screening by the Mood Disorder Questionnaire (MDQ) was positive, or if they had reported a physician’s diagnosis of bipolar diagnosis and depression.

¶Respondents considered “unipolar depressed” reported a diagnosis of depression, had a negative MDQ screening, and did not report a diagnosis of bipolar disorder.
ness in the treatment of patients with bipolar disorder have appeared.29

Olanzapine, the atypical antipsychotic agent most closely related to clozapine, received FDA approval as a monotherapy agent for the treatment of patients with acute mania in 2000 and as an adjunct treatment to lithium or valproate sodium in 2003. More important than its usefulness in the treatment of patients with mania, olanzapine has demonstrated efficacy in maintenance in two large 12-month trials involving olanzapine versus placebo and olanzapine versus lithium.30,31

In the trial comparing it with placebo, olanzapine was statistically superior to placebo in depression and mania relapse rates. In the trial comparing it with lithium, olanzapine was statistically comparable to lithium at preventing depressive relapse and was statistically superior to lithium at preventing manic relapse. In 2004, based on the strength of these two trials, olanzapine received an FDA-approved indication for the maintenance of response in patients with bipolar disorder.

Olanzapine and the combination of olanzapine and fluoxetine were studied in two 8-week placebo-controlled registration trials to assess efficacy in patients with acute bipolar depression.17 In both studies, olanzapine monotherapy clearly exerted an early and sustained antidepressant effect. In contrast, the combination treatment of olanzapine and fluoxetine separated statistically from placebo at every visit including week 1. In addition, the combination treatment also separated from its component monotherapy of olanzapine at weeks 4 through 8.

Based on these investigations, the olanzapine-fluoxetine combination became the first FDA-approved treatment for patients with acute bipolar depression. In a short time, olanzapine has become the most thoroughly investigated molecule in bipolar disorder, resulting in four FDA indications. Therefore, olanzapine and the olanzapine-fluoxetine combination are reasonable for first-line treatment of patients with bipolar disorder for the following reasons: Ease of use, simple and flexible dosing, and established bidirectional efficacy in both acute phases, as well as in maintenance.

Olanzapine has no black box warnings, and routine blood monitoring is not necessary. The most frequent adverse events associated with olanzapine include somnolence, increased appetite, and weight gain.

Other atypical antipsychotic agents also are being studied in patients with bipolar disorder. Although risperidone and quetiapine fumarate received FDA approval as monotherapy and adjunct treatment for patients with acute mania, current evidence does not support their use in patients with acute bipolar depression or in maintenance.

Comment

Remembering the following summary points will not only assist the clinician in accurately detecting patients with bipolar disorder, but should also result in better treatment outcomes for all depressed patients:

- Always consider unipolar depression as a diagnosis of exclusion. First rule out medical and substance-induced etiologies, as well as bipolar disorder.
- Remember that bipolar disorder is primarily a disease of depression. Thirty percent of patients with depression seen by primary care physicians have bipolar disorder.
- Be aware of the five features of diagnosis from the bipolar diagnostic star. This awareness will increase sensitivity to the recognition of patients with bipolar disorder.
- Consider using a screening instrument for bipolar disorder (eg, the MDQ).
- Do not be misled by patients’ chief complaint, as bipolar disorder is frequently accompanied by comorbidities. Patients with identified substance abuse, anxiety disorders, and ADHD are an enriched population for bipolar disorder.
- Note that antidepressant monotherapy is contraindicated in patients with bipolar disorder, and in some cases, may mobilize mania or induce cycling.
- Be guided by FDA indications, as well as results of controlled trials, when selecting mood stabilizers; all mood stabilizers are not equally effective, nor are they all bidirectional.
- Familiarize yourself with the use of the only FDA-indicated treatment for patients with acute bipolar depression, the combination of olanzapine and fluoxetine.
- Be mindful of tolerability issues when selecting any psychotropic medication, and monitor patients accordingly.
- Consider bipolar disorder a chronic, progressive disease state. As such, the selection of mood stabilizers, as well as a

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Figure 3. Pharmacologic agents and their indications approved by the US Food and Drug Administration for treatment of patients with bipolar disorder.

- Lithium
  - Indicated for acute mania and prevention of relapse
  - Black box warning, as well as other safety risks
  - Requires therapeutic blood monitoring
- Lamotrigine
  - Indicated for maintenance of response
  - One black box warning
  - Risk of rash and Stevens-Johnson syndrome
- Divalproex Sodium
  - Indicated for the treatment of acute mania
  - Three black box warnings
  - Requires therapeutic blood monitoring
- Olanzapine
  - Indicated for the treatment of acute mania and in combination with divalproex or lithium for acute mania
  - Indicated for monotherapy for the maintenance of treatment response for bipolar disorder
  - Indicated in combination with fluoxetine hydrochloride for the treatment of bipolar depression
  - Warning concerning the monitoring of diabetes for all atypical antipsychotics
- Risperidone and Quetiapine Fumarate
  - Indicated for the treatment of acute mania and as combination therapy with divalproex or lithium for acute mania
  - Warning concerning the monitoring of diabetes for all atypical antipsychotics

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strong therapeutic alliance, will lead to the most satisfactory long-term outcome.

References


