A new understanding of the symptoms and treatment of bipolar disorder has emerged during the past decade. Previously, bipolar disorder was perceived to be a fairly rare illness, with one basic type of symptomatology, denoted by its previous name manic-depressive disorder. Investigation and delineation of a wide spectrum of conditions have led to appreciation that bipolar disorder is quite common, possibly affecting 2.2 million American adults.¹

Bipolar disorder is no longer an illness limited to diagnosis and management by the psychiatric profession. Overall, data suggest that only a third of all patients with mental illness are treated in the mental health sector, while approximately half of all patients with mental illness are seen by primary care physicians.² As are patients with major depression and other mood disorders, most patients with bipolar disorder are likely receiving treatment in the primary care setting. Treating patients with bipolar disorder in primary care has several distinct advantages, including earlier initiation of treatment, smooth continuity of care, and an established therapeutic alliance.

The diagnosis and treatment of bipolar disorder is not without challenges. Even psychiatric caregivers often misdiagnose bipolar disorder with predictably poor outcomes of treatment. The purpose of this article is to better define...
the characteristics of the spectrum of bipolar disorder, describe a diagnostic approach, and summarize the agents approved for the treatment of patients with this illness.

**Bipolar Disorder**

Bipolar disorder may be better known to many physicians as manic-depressive disorder. However, the classic presentation denoted by this older term is limited only to one form of bipolar disorder, bipolar I. Indeed, bipolar disorder is actually several conditions with overlapping symptomatology. This spectrum includes bipolar I and bipolar II, cyclothymic disorder, and bipolar not otherwise specified (NOS).3

These different forms of bipolar disorder vary in prevalence. The lifetime prevalence of bipolar I disorder is estimated to be approximately 1.0% to 1.5% and is roughly equivalent in men and women. Bipolar II is less common, as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition text revision (DSM-IV-TR) criteria,3 with a prevalence of 0.5%. The DSM-IV-TR criteria, however, may be overly restrictive; some estimates of bipolar II using more liberal criteria suggest that it may be the most common form of the disorder.

Bipolar II is also up to twice as common in women than in men.4 Estimates of the prevalence of the full bipolar spectrum give a sense of how common the disorder may be, ranging from 3.0% to 6.5% of the general population.5

Patients with bipolar disorder may have a wide variety of symptoms when they first seek medical care. These complaints may include depression, anxiety, mood swings, euphoria, pressured speech, impulse control problems, substance abuse, legal trouble, fatigue, grandiosity, or increased activity.

Other conditions may overlap with bipolar disorder and can confuse the proper diagnosis. Major depression is the most common misdiagnosis of bipolar disorder, including treatment-resistant, agitated, and atypical depression. Bipolar disorder may also be mistakenly diagnosed as other conditions, including schizoaffective disorder, cluster B personality disorders (eg, borderline personality, antisocial personality), and postpartum depression.

Attention-deficit hyperactivity disorder (ADHD) is highly comorbid with bipolar illness. As many as 30% of patients with ADHD may have bipolar disorder. Substance abuse issues are also common. One study reported a 46% rate of alcohol abuse in patients with bipolar disorder, compared with 21% in patients with unipolar depression. The prevalence of drug abuse was similar to that of alcohol abuse: 41% in patients with bipolar disorder and 18% in patients with unipolar depression.6

A range of anxiety disorders is also highly comorbid with bipolar disorder, including obsessive-compulsive disorder, panic disorder, generalized anxiety disorder, and various phobias (Figure 1).

**Frequent Misdiagnosis of Bipolar Disorder**

It should not be surprising, given this range of symptoms and comorbid conditions, that bipolar disorder is often misdiagnosed. The most common incorrect diagnosis is major depression.

Bipolar disorder is commonly mistaken for unipolar depression for several reasons. First, patients are more likely to seek clinical help during the depressive phase of their illness rather than during the manic phase. Further, more than 50% of all patients with bipolar disorder have a major depressive episode before they experience a manic episode.7 Research suggests that 30% of patients who have depressive symptoms may have some form of bipolar disorder.8,9

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The rate of misdiagnosis in bipolar disorder is exceptional. In 2000, the Depression and Bipolar Support Alliance (formerly called the National Depressive and Manic Depressive Association) surveyed its membership to assess the rate of misdiagnosis. In all, 7 of 10 respondents had their disorder initially misdiagnosed by a mental health specialist. Respondents had an average of 3.5 misdiagnoses and four consultations before receiving an accurate diagnosis. More than a third sought help repeatedly for 10 years or more before their illness was accurately diagnosed.

Misdiagnosis has a significant impact on patients' lives. Inadequate treatment perpetuates the symptoms of bipolar disorder with negative consequences for the course and outcome of the illness and the patients' quality of life. The symptoms of bipolar disorder may worsen over time in the absence of proper treatment. Individuals with bipolar disorder are also at significant risk of suicide. Other potential impacts include the direct and indirect costs related to health care services and lost productivity.

Detecting Bipolar Disorder
A large proportion of patients with depressive symptoms are likely to have a form of bipolar disorder. Detecting the symptoms or history of mania or hypomania in these patients can be difficult. A mnemonic, DIGFAST (Figure 2), may be helpful to remember the key symptoms of mania: distractibility, indiscretion or disinhibition, grandiosity, flight of ideas, activity increase, sleep deficit or decreased need for sleep, and talkativeness. In addition to screening patients with questions about these symptoms, physicians should also consider speaking with the patients' families.

A new instrument can be helpful in the diagnosis of bipolar disorder. The Mood Disorder Questionnaire (MDQ) is a brief patient self-report covering 13 different manic symptoms to which patients note “yes” or “no” answers. Seven or more positive responses on the MDQ, indicating the presence of concurrent manic symptoms and a moderate level of impairment, are highly suggestive of a bipolar illness.

Because patients often underreport their symptoms, especially their manic or hypomanic symptoms, instruments such as the MDQ (available on several Web sites, including that of the Depression and Bipolar Support Alliance at: http://www.dbsalliance.org/questionnaire/screening_intro.asp) can be helpful in establishing a diagnosis of bipolar disorder. A score of seven or more positive responses is consistent with a diagnosis of a bipolar disorder. In addition to achieving the threshold number of symptom items, the patient must also have indicated that the symptoms clustered in the same time (“yes” on question 2 of the MDQ) and caused moderate or serious problems (“moderate” or “serious” on question 3).

Figure 3 provides a patient self-survey that is derived from the MDQ.

The Bipolar Spectrum
The defining characteristic of bipolar illness is its duality: periods of depressive symptoms and periods of manic symptoms. The duration and severity of each of these phases determines the specific bipolar diagnosis. The criteria for the diagnosis of mania include a period of at least 1 week (or less if hospitalization is required) during which the patient has an abrupt and persistently elevated, expansive, or irritable mood. Importantly, these symptoms must cause a marked impairment in social or occupational functioning; alternatively, they may be characterized by the presence of psychotic features.
Another common feature of bipolar disorder is the mixed episode. During such a period, patients meet the criteria for both major depression and mania nearly every day for at least 1 week. These individuals have rapidly alternating moods and frequently display agitation, insomnia, changes in appetite, racing thoughts, suicidal thoughts, and psychotic features.12

Bipolar I Disorder
Diagnosis of bipolar I disorder—the classic manic-depressive disorder—requires a history of at least one manic or mixed episode in addition to a major depressive episode. Onset tends to occur in younger people, with a mean age of onset for a first manic episode in the early 20s. Mixed states occur in approximately 40% of patients. Bipolar I also has a strong familial component, and patients with a mood disorder and a strong family history of bipolar disorder should be carefully screened for bipolar I. As with many mood disorders, bipolar I presents a significant burden for patients and the rates of substance abuse and suicide are high. Approximately 60% of patients with bipolar I have comorbid substance abuse issues, and 10% to 15% commit suicide.3

Bipolar II Disorder
Type II bipolar disorder refers to major depression and recurrent hypomania, which is characterized by milder manic symptoms than are seen in the full-blown mania of bipolar I disorder. Often, patients with bipolar II will not consider periods of hypomania to be abnormal and may describe themselves as feeling “normal” or “energetic.” Many recall hypomanic states as periods of great productivity. Some will not even remember previous hypomanic periods during depressed phases of the illness. Because of these limitations, physicians may find it useful to gather information from other people in a patient’s life, such as the spouse or other family members.

According to the DSM-IV-TR,3 a diagnosis of hypomania requires a distinct period of at least 4 days during which the patient exhibits an abnormally and persistently elevated, expansive, or irritable mood. Hypomania is associated with an unequivocal change in mood and functioning, but it is not severe enough to cause marked impairment in social or occupational functioning. Psychotic features are not present in hypomania.

Evidence suggests that these criteria may be insensitive for detecting bipolar II; however, the mean modal duration of hypomania, for example, is only 1 to 3 days, suggesting that the prevalence of bipolar II may be far greater than currently estimated. Phenomena that may be more predictive of bipolar II include mood lability, energetic-active depression, social anxiety, and intense daydreaming. A typical bipolar II hypomanic episode is an emotional roller coaster ride: the patient’s mood descends from “normal” to “depression,” then ascends to brief periods of hypomania (24 to 72 hours), mixed-state symptoms may develop, then the patient’s mood descends back to the depressed state (Figure 4).

Cyclothymic Disorder
Cyclothymic disorder is characterized by hypomania and depressive symptoms that do not meet the threshold for major depression. A diagnosis of this bipolar spectrum illness requires the presence of numerous periods with hypomanic symptoms and numerous periods with depressive symptoms (but not major depression) for at least 2 years. During this time, the patient must not be symptom-free for more than 2 months at one time. The symptoms also must cause clinically significant distress or impairment in social, occupational, or other key areas of functioning. Patients
with cyclothymia have a 15% to 50% risk of the development of more severe forms of bipolar disorder (type I or II).

Bipolar Disorder Not Otherwise Specified
Patients who display bipolar features but do not meet the criteria for any specific form of bipolar disorder may be classified as bipolar NOS. Examples include:
- patients who have rapid alternations between manic and depressive symptoms but do not meet the duration criteria for other forms of bipolar disorder;
- patients with recurrent hypomania but without intercurrent depression; and
- patients with hypomanic and depressive episodes that are too infrequent to qualify for cyclothymic disorder.

Other Diagnostic Elements
Several often-overlooked criteria can further assist in the correct diagnosis of bipolar disorder. For example, unlike depression and other unipolar disorders, bipolar disorder commonly runs in families. The strongest indicators are a history of relatives in three consecutive generations or three or more relatives in one generation with recurring mood disorders.

Also common is a history of poor response to antidepressant therapy. The unsuccessful use of several antidepressants is highly suggestive of bipolar disorder. Treatment failure in these patients may be characterized by increased agitation, restlessness, or insomnia. Treatment-emergent hypomania may develop, generally within the first 2 weeks of antidepressant therapy, often beginning and ending abruptly and sometimes showing mixed features. Other patients may have worsening depression with antidepressant treatment. Thus, erratic or uneven response to antidepressants, multiple antidepressant failures, and the emergence of manic symptoms all suggest a bipolar illness.

Other characteristic features of bipolar disorder include a high risk for postpartum depression in women. Indeed, women with bipolar disorder are sensitive to the postpartum state, and bipolar disorder should be considered as a possibility in every woman who has postpartum depression, particularly if it is her first episode of major depression.

Certain specific types of behaviors may raise suspicion of bipolar disorder. Common among these behaviors is the mixed quality of both depression and energy. For example, a person who has depression and is having an affair, or someone who is both suicidal and pursuing a project (such as building a house or planning a vacation) may raise suspicion of bipolar disorder. Other examples might include patients with major depression who dress extravagantly or have other attention-getting features such as dyed hair, multiple body piercings, or tattoos.

Five Key Factors
Five key factors should be kept in mind in the diagnosis of bipolar disorder.

- First is age of onset: Bipolar illness often begins in childhood or adolescence.
- Second is family history: Bipolar disorder is characterized by a pedigree (three or more first-degree relatives with a mood disorder, or three consecutive generations with evidence of a mood disorder).
- Third is the presence of mania or hypomania: Even in the depressive phase, patients with bipolar disorder can be energized and highly active.
- Fourth is cycling of mood: Patients with bipolar disorder can switch rapidly from a manic or hypomanic state to a depressed state or vice versa.
- Fifth is response to treatment: Antidepressants do not work well in most people with bipolar disorder, often inducing manic symptoms.

Treating Patients With Bipolar Disorder
The American Psychiatric Association (APA) published practice guidelines for the treatment of bipolar disorder in 2002. These guidelines recommend a series of steps to follow before choosing treatment, including a thorough diagnostic evaluation of the patient, an assessment of the safety of the patient (and others), and establishing a therapeutic alliance with the patient. Also important to successful treatment are several non-pharmaceutical approaches, including the promotion of regular patterns of activity and sleep, anticipation of stressors that may induce mania or depression, the early identification of new episodes, minimizing functional impairments, and providing education to the patient and family regarding the nature of bipolar disorder and its treatment.

Mood stabilizers are the mainstay of therapy for bipolar disorder. An ideal primary mood stabilizer reduces acute manic symptoms, does not induce depression, and prevents future relapses of mania or depression. According to the APA, the treatment of less-ill patients can be accomplished via monotherapy with the mood stabilizers lithium, divalproex sodium, or olanzapine. Patients with more severe manic or mixed episodes may require lithium or divalproex sodium, or olanzapine.
proxe plus an atypical antipsychotic agent. The APA guidelines recommend lithium and lamotrigine for the depressive phase of the illness, with adjunctive antipsychotics or electroconvulsive therapy (ECT). Lithium, divalproex, and olanzapine may each be used for maintenance treatment, though lithium is particularly useful for the long-term prevention of recurrence of mania and bipolar depression. Only 20% to 25% of patients with bipolar disorder are stabilized with monotherapy.

Although many agents have been used in the treatment of patients with bipolar disorder and two have recently received US Food and Drug Administration (FDA) approval, discussion here will be limited to four effective, earlier FDA-approved pharmacologic agents—lithium, divalproex, lamotrigine, and olanzapine. The atypical antipsychotic risperidone, used alone or in combination with lithium or divalproex, received FDA approval for acute bipolar mania and mixed episodes in December 2003. In addition, the atypical antipsychotic quetiapine fumarate, used as monotherapy or as adjunct therapy with lithium or valproate, received FDA approval for acute bipolar mania in January 2004 (Table). Other atypical agents also are under consideration by the FDA.

### Lithium
Lithium is indicated for the treatment of patients with acute mania and for maintenance treatment. Lithium has demonstrated response rates of up to 70% in clinical trials, with an onset of action of between 5 and 21 days. It is not effective in rapid cycling or mixed states, however, and carries a black box warning and other safety risks. Use of lithium requires periodic therapeutic blood monitoring, with target blood levels of 0.6 mEq/L to 1.5 mEq/L. Blood levels should be monitored twice per week until the patient’s condition is stabilized.

Lithium is recommended as a first-line agent for the maintenance treatment of patients with bipolar disorder. Importantly, lithium has demonstrated significant reductions in suicide risk with long-term use. Blood monitoring is required less often once the patient is stabilized; it is recommended at least every 3 to 4 months. Thyroid and renal function also should be monitored when lithium is used. Potential adverse events include weight gain, hypothyroidism, acne, nausea, polydipsia, polyuria, cognitive dulling, teratogenicity, and drowsiness, among others.

### Lamotrigine
Lamotrigine is a mood stabilizer that was recently approved by the FDA for use in conjunction with standard therapy for bipolar disorder to help delay the time between mood episodes. As with lithium, lamotrigine carries a black box warning, though monitoring of the serum level is not required. The warning covers the potential for serious rash, or Stevens-Johnson syndrome. Nonserious rash also occurs in 10% to 20% of patients. Because of these concerns, lamotrigine must be carefully titrated to therapeutic levels. Otherwise, lamotrigine is well tolerated with only mild, nonspecific side effects.

Drug interactions have been described with lamotrigine, including divalproex and oral contraceptives. Owing to the potential for clinically significant interactions, the dose of lamotrigine should be carefully adjusted in patients also taking divalproex, oral contraceptives, or other drugs that affect the metabolism of lamotrigine. Prescriptions for the proprietary name of lamotrigine (Lamictal) need to be written clearly to

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**Table**

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<th>Agent</th>
<th>Manic</th>
<th>Mixed Episode</th>
<th>Psychotic</th>
<th>Rapid Cycling</th>
<th>Cognition</th>
<th>Bipolar Depression</th>
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**Key:** + indicates at least one well-controlled trial with positive results; ++, two or more well-controlled trials with positive results; +/−, mixed (positive and negative) results; −, trials with negative or failed results.


†Not approved by the US Food and Drug Administration for bipolar disorder.
avoid dispensing errors. Such errors have occurred between this drug and the generic or brand names of other medications (eg, Lamisil, lamivudine, Ludiomil, labetalol, and Lomotil).17

Divalproex
Divalproex is indicated for the treatment of patients with acute mania. This agent also is associated with potential side effects, carries three black box warnings, and requires therapeutic blood monitoring. Therapeutic serum levels range from 50 ng/mL to 125 ng/mL. When initiating patients on divalproex therapy, a loading dose of between 20 mg per kilogram of body weight and 30 mg per kilogram of body weight should be used.

Adverse effects associated with divalproex include both dose-related and nondose-related effects. Dose-related effects include nausea, diarrhea, fatigue, drowsiness, thrombocytopenia, and cognitive dulling. Nondose-related effects include weight gain, tremor, hair loss, pancreatitis, hepatotoxicity, and teratogenicity.

Olanzapine
Olanzapine, an atypical antipsychotic, is indicated for use as monotherapy or in combination with lithium or valproate for acute manic or mixed episodes. In December 2003, the olanzapine-fluoxetine combination was the first drug to be approved for bipolar depression, and in January 2004, olanzapine received FDA approval for maintenance treatment to delay relapse into either mania or depression. This agent is generally safer, as it has no black box warnings and does not require blood monitoring. Current APA guidelines recommend olanzapine as a first-line agent for the treatment of patients with the acute manic or mixed phases of bipolar disorder. Studies of olanzapine in maintenance treatment suggest that it is equally effective as lithium or divalproex.18-20

Olanzapine is easier to dose than other bipolar medications. It is available in once-daily dosing. A common starting dose for bipolar mania is 15 mg orally at bedtime. Potential adverse effects include weight gain, dry mouth, dizziness, drowsiness, edema, and effects on glucose metabolism. Because of the risk for metabolic effects, patients should be monitored before and during treatment for fasting blood glucose levels.

Comment
Bipolar disorder is common in the general population and in the primary care setting. It can be difficult to diagnose, is often misdiagnosed, and therefore is inappropriately treated. However, the use of screening tools such as the MDQ10 and careful attention to symptoms, patient and family histories, and responses to treatment can improve the detection and assessment of bipolar disorder. Four mood stabilizers currently are approved for the treatment of patients with bipolar disorder: lithium, divalproex, lamotrigine, and olanzapine.

Primary care physicians should be aware of the high rate of bipolar disorder among the patients in their practices and the possibility that many patients in whom depression has been diagnosed may actually have bipolar disorder. Proper treatment of these patients can reduce the burden of illness and the cost of therapy. Future research will further elucidate means for discriminating among mood disorders and the best treatment course for different patient types.

References