Bipolar Disorder
Recognizing and Treating in Primary Care

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Primary care clinicians are often the first point of contact for persons with bipolar disorder. Unfortunately, delays in diagnosis are common, as many of these patients are misdiagnosed with unipolar depression on initial presentation. Since an early and accurate diagnosis may reduce the burden of bipolar disorder and improve outcomes, clinicians should be able to recognize its symptoms and initiate treatment of this deceptive disorder.

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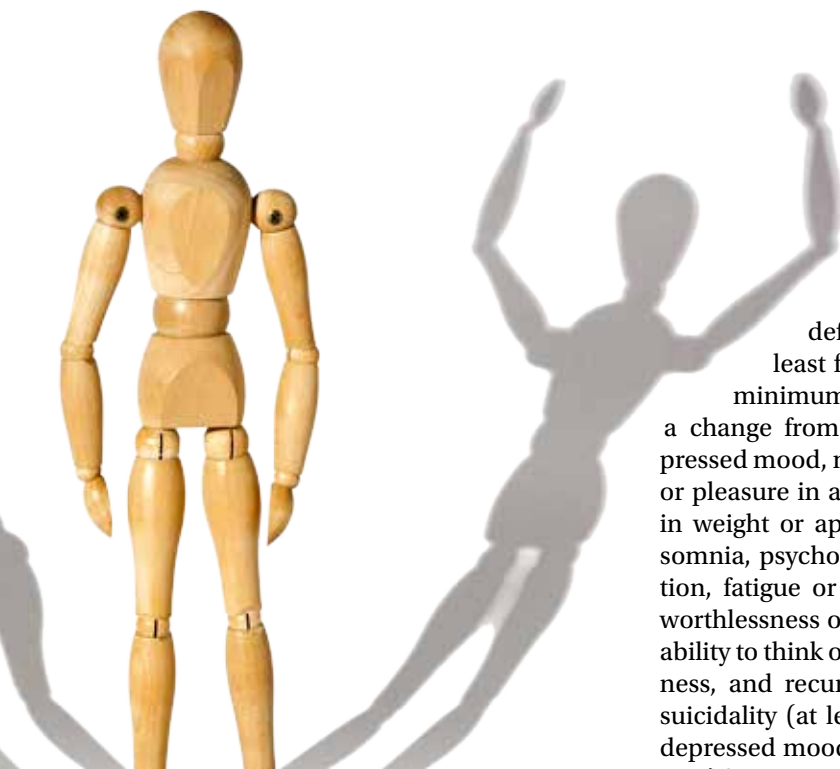
LEARNING OBJECTIVES

- Define bipolar disorder according to the *DSM-5* criteria.
- Recognize how patients with bipolar disorder can present to their primary care provider.
- Discuss how to perform a clinical and psychiatric evaluation on patients with suspected bipolar disorder.
- Describe the therapeutic options for a patient with bipolar disease in a primary care setting.

B ipolar disorder is a chronic mental illness characterized by fluctuations in mood and energy that manifests as recurrent episodes of manic or depressive symptoms. It is estimated that between 10% and 38% of patients with bipolar disorder receive all their mental health care in a primary care setting.[1] Although patients with bipolar disorder often initially present to their primary care provider, they frequently go undiagnosed because of the complexity of the disorder's symptomatology and a low index of suspicion among primary care providers.[2] Comorbid medical conditions and psychiatric issues can also lead to misdiagnoses.

Because primary care providers are often the first point of contact for patients with bipolar disorder, they are well positioned to recognize bipolar symptoms early in the course of the illness. The pure subtypes of bipolar disorder include bipolar I and bipolar II. Clinicians who work in a primary care or emergency department setting should be able to recognize and initiate treatment for these two subtypes while the patient is waiting for a psychiatric evaluation. Accurate early diagnosis of this disabling disorder can reduce morbidity and improve outcomes by allowing for appropriate referral, pharmacotherapy, and psychotherapy.

DEFINITION

According to the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*), bipolar disorder is a

ers but does not cause marked impairment, need for hospitalization, or psychosis. MDE is defined by the presence of at least five of nine symptoms for a minimum duration of two weeks and a change from previous functioning: depressed mood, markedly decreased interest or pleasure in activities, significant change in weight or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or excessive guilt, decreased ability to think or concentrate or indecisiveness, and recurrent thoughts of death or suicidality (at least one symptom must be depressed mood or loss of interest or pleasure).[3]

EPIDEMIOLOGY

Bipolar disorder affects men and women equally. It can occur at any age but is seen most commonly in persons younger than 25.[4] The mean age at the first manic/hypomanic or major depressive episode was determined to be 18.2 in bipolar I and 20.3 in bipolar II.[5] The lifetime prevalence of bipolar disorder in the United States is around 4%, with one study finding prevalence estimates of 1.0% for bipolar I disorder and 1.1% for bipolar II disorder.[5]

Bipolar disorder is common among primary care patients with depression. Two studies that explored the risk for bipolar disorder among depressed outpatients in primary care settings found that between 20% and 30% of these patients screened positive for bipolar disorder on the Mood Disorders Questionnaire (MDQ), indicating that a more thorough evaluation for bipolar disorder was needed.[6,7] A systematic review of the literature found similar rates of positive results on the MDQ screening measure among primary care patients with depression, a trauma exposure, medically unexplained symptoms, or a psychiatric complaint; bipolar disorder was diagnosed with a structured clinical interview in 3% to 9% of these patients.[8] Children of parents with bipolar disorder have a 4% to 15% risk for also being affected.[4]

mood disorder defined by episodes of mania, hypomania, and major depression.[3] Patients with bipolar I disorder experience manic episodes and almost always experience major depressive and hypomanic episodes. Bipolar II disorder is marked by at least one hypomanic episode, at least one major depressive episode (MDE), and the absence of manic episodes.[3] A manic episode is at least one week of abnormally and continually elevated, expansive, or irritable mood and increased activity or energy accompanied by at least three of the following symptoms (or four if mood is only irritable): inflated self-esteem, decreased need for sleep, increased talkativeness, flight of ideas or racing thoughts, marked distractibility, increased goal-directed activity or agitation, and excessive involvement in dangerous or high-risk activities (eg, reckless spending or increased sexuality). To be considered a manic episode, the mood disturbance must cause marked impairment in social or occupational functioning, result in hospitalization, or involve psychotic features, and the symptoms cannot be attributable to the effects of drugs or medications or another medical condition.[3]

In a hypomanic episode, the period of elevated or irritable mood lasts for a shorter duration (at least four days); is associated with a clear, uncharacteristic change in functioning; and is observable by oth-

TABLE 1
Medications for Patients with Bipolar Disorder

Drug/Drug class	Dosage (therapeutic range)	Adverse effects and toxicity	
Lithium	900-1,800 mg/d po (titrate to trough serum levels of 0.8-1.2 mEq/L)	Acute: nausea, loose stools, weight gain, cognitive impairment, and polyuria/thirst Chronic: renal and thyroid dysfunction	
Valproate, divalproex	1,500-2,500 mg/d po titrated from 250 mg bid	Weight gain, nausea, vomiting, hair loss, easy bruising, tremor, dizziness, thrombocytopenia FDA boxed warnings regarding hepatotoxicity, pancreatitis, and fetal risk	
Carbamazepine	800-1,000 mg/d po titrated from 200 mg QD or bid	Drug interaction due to induction of P450 liver enzymes Drowsiness, dizziness, blurred or double vision, lethargy, headache, leukopenia, nausea, vomiting, diarrhea, hyponatremia, fluid retention, pruritus FDA boxed warning of rash, including SJS and TEN*	
Antipsychotics **Aripiprazole** **Asenapine** **Haloperidol** **Lurasidone** **Olanzapine** **Quetiapine** **Risperidone**	Dosage based on medication	Somnolence, dry mouth, orthostatic hypotension, extrapyramidal effects, akathisia, tardive dyskinesia (more common with typical antipsychotics such as haloperidol), neuroleptic malignant syndrome, hyperprolactinemia More common with atypicals: weight gain, hyperglycemia, metabolic syndrome, dyslipidemia, sexual dysfunction	
Lamotrigine	200 mg/d po Begin with 25 mg/d, titrate dose over 6 wk	Dizziness, tremor, somnolence, headache, dry mouth, nausea FDA boxed warning of severe rashes, including SJS and TEN Reported hematologic effects (eg, neutropenia, leukopenia, thrombocytopenia, pancytopenia, anemia; rarely, aplastic anemia and pure red cell aplasia)	

Abbreviations: CBC, complete blood count; LFT, liver function test; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; TSH, thyroid-stimulating hormone.
*Per FDA boxed warning, HLA-B*1502 allele is a marker for carbamazepine-induced SJS and TEN (estimated incidence 5%), which occurs almost exclusively in patients of Asian ancestry.[20]
Sources: Culpepper. *Prim Care Companion CNS Disord.* 2014[2]; Price and Marzani-Nissen. *Am Fam Physician.* 2012.[4]

CLINICAL PRESENTATION IN PRIMARY CARE

Bipolar patients are often depressed or euthymic for a majority of their lives but can also present in a manic or hypomanic state. In primary care settings, these patients often present with depression (including postpartum depression), which can obscure the diagnosis. Misdiagnosis of bipolar disorder as recurrent unipolar depression occurs in 60% of patients seeking treatment for depression.[9]

Patients with bipolar disorder who present to primary care usually demonstrate a wide range of mood symptomatology other than depression, including mood swings,

Role in therapy	Monitoring
Acute mania stabilization, maintenance Bipolar depression	Lithium every 3 mo; sodium serum level, renal function, TSH every 6-12 mo
Acute mania and rapid cycling, maintenance	LFTs and CBC with platelet count frequently at initiation, then every 3-12 mo Serum valproate level frequently at initiation, then every 3-6 mo Suicidality
Acute manic or mixed episodes, stabilization and maintenance	CBC and LFTs monthly for 2 mo, then every 3-6 mo Serum carbamazepine level every 1-2 wk initially, then every 3-6 mo Serum sodium level
Acute mania and depression Olanzapine, quetiapine, lurasidone: bipolar depression alone or in combination with mood stabilizers Olanzapine, quetiapine, risperidone: maintenance	Weight, waist circumference. CBC, fasting lipids and glucose at baseline, monthly for first 3 mo, then every 6 mo
Bipolar depression (maintenance)	CBC and LFTs monthly for the first 2 mo, then every 3-12 mo Rash in initial course of therapy and more frequently with concurrent use of valproate

anxiety, fatigue, sleep disturbances, and the inability to focus or concentrate. Patients can also present in mixed states. These are characterized by elements of irritability, increased energy, and sleeplessness with depressive features.

Several clues that can assist in detecting bipolar disorder relate to age at onset, family history, mood shifts, seasonality, and atypical depressive symptoms (eg, sleep dysregulation and appetite changes). Although the diagnosis of bipolar disorder is commonly delayed by many years, patients often report significant mood symptoms in their early 20s. In a study that used a self-administered questionnaire to assess the experience of persons living with bipolar disorder, 33% of the respondents were younger than 15 when their symptoms first started, 27% were between 15 and 19, and 39% were 20 or older.[9] Parental and family history of bipolar disorder increases risk for the disorder in offspring, so a thorough family history is essential when the disorder is suspected.

Aside from the classic presentation de-

fined by the *DSM-5* criteria, patients with bipolar disorder can also exhibit other effects of their illness, such as alcohol-related problems and sexually transmitted or drug-related infections. In patients with bipolar disorder, rates of alcohol use range from 21.4% in adults to 54.5% in adolescents and young adults.[10] Social history may reveal relationship and marital issues, financial problems, difficulties keeping a job, and legal problems.[9,11] Suicide attempts and completed suicides are significantly more common among persons with bipolar disorder than among the general population.[12,13]

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Comorbidity with at least one other disorder is common in bipolar disorder.[5] The most common comorbid personality disorder associated with bipolar disorder is borderline personality disorder, which is characterized by ongoing instability in moods and behavior. Persons with this disorder can experience intense episodes of anger, depression, and anxiety that may last from hours to days. The high prevalence of persistent symptoms despite treatment in bipolar disorder and the unstable and partly remitting course of borderline personality make it difficult to distinguish between the two disorders.[14] The frequent mood changes that occur with borderline personality disorder may appear to overlap with the mood swings characterizing bipolar disorder, but the mood episodes in borderline personality disorder are of shorter duration than those in bipolar disorder. Other common comorbid disorders seen in patients with bipolar disorder include substance abuse disorders, anxiety disorders (especially panic disorder, generalized anxiety disorder, and obsessive-compulsive disorder), and attention-deficit/hyperactivity disorder.[5]

Primary care providers should be aware of other common comorbidities that may be present in patients with bipolar disorder. These patients commonly experience medical problems such as diabetes, obesity, and metabolic syndrome, which all lead to increased cardiovascular risk.[15-17]

CLINICAL EVALUATION

The initial clinical evaluation of the patient should include a thorough medical, social, family, and psychiatric history. Medical conditions that may mimic bipolar disorder include neurologic conditions (eg, partial seizures, neoplasm, strokes, dementia, delirium) and endocrine disorders (eg, Cushing disease, hyperthyroidism/hypothyroidism), as well as vitamin deficiencies (B_{12}, folate, niacin, thiamine) and drug and substance use/misuse (alcohol, drugs including antidepressants and stimulants).[4] All patients should have a baseline complete physical examination, including neurologic and mental status examinations. Diagnostic tests to assess for potential differential diagnoses and evaluate baseline levels include the following:

- Basic metabolic panel, including fasting glucose, to evaluate electrolytes and risk for diabetes or Cushing disease, and to assess baseline renal function
- Thyroid function tests
- Complete blood count to assess status prior to anticonvulsant treatment (eg, carbamazepine)
- Pregnancy test if applicable (prior to use of medications)
- Liver function tests to assess baseline measurements prior to use of medications
- Electrocardiography in patients older than 40 to establish baseline and assess QTc interval, especially with use of antipsychotics and carbamazepine
- Urine toxicology screen (to rule out substance abuse).

PSYCHIATRIC EVALUATION

Psychiatric evaluation should focus on age at onset of symptoms, the presence of hypomanic or manic symptoms, prior response to antidepressants, course of the disease including history and duration of

depression or manic/hypomanic episodes, and sleep disturbances (increased during depressive episodes and significantly decreased during manic episodes). It is important to assess for a history of self-harm, suicidal ideation, suicide attempts, hospitalizations, legal issues, multiple career shifts, marriage and relationship issues, and smoking and alcohol/substance misuse. Patients with severe manic or depressive episodes may experience psychotic features such as grandiose or paranoid delusions and hallucinations. A history of symptoms from close family members or friends can assist in the diagnosis of bipolar patients.

The use of *DSM-5* criteria, as summarized earlier, improves the accuracy of bipolar diagnosis.[3] In addition, validated tools are available to help clinicians screen for bipolar disorder, although it is important to remember that a positive screening result is not sufficient to establish a bipolar disorder diagnosis. A widely used instrument that has been validated for screening for bipolar disorder is the MDQ (available at **www.dbsalliance.org/pdfs/MDQ.pdf**). This self-report questionnaire consists of 15 questions that assess hypomanic or manic symptoms and functional impairment. The first 13 questions of the MDQ screen for a lifetime history of *DSM*-based hypomanic or manic symptoms. The last two questions ask whether these symptoms occurred at the same time and whether they caused dysfunction in various domains, such as work and family life. The MDQ is considered positive if a patient endorses at least seven of the symptom items, indicates that symptoms have occurred at the same time, and rates their dysfunction in life domains as "moderate" or "serious." As a screening tool, the MDQ has a reported sensitivity of 73% and a specificity of 90% for bipolar disorder.[11] This questionnaire can and should be used by primary care providers to help determine if their patient is at risk and requires a comprehensive evaluation for bipolar disorder.

Notably, even after a clinician has properly diagnosed bipolar disorder, patients and family members are often reluctant to commence treatment due to the stigma associated with mental health disorders.[18] To help offset the effects of stigma, patients should be referred for psychologic counseling, including family counseling.

MANAGEMENT

Management of bipolar disorder in the primary care setting includes psychiatric and psychologic counseling referrals. Primary care providers must know the medications used to treat bipolar disorder and their related adverse effects, toxicities, warnings, and drug interactions, as they may treat bipolar patients for other medical conditions. Early diagnosis and treatment/referral can improve prognosis and reduce the risk for relapse and subsequent disability.[19] Inpatient management is generally recommended for severe manic episodes, psychotic episodes, patients who present a danger to themselves or others, and patients with suicidal or homicidal ideations/actions.

Medications are the primary treatment for all stages of bipolar disorder, and choice of medications is based on stage, previous response, and adverse effect profiles (see Table 1, pages 44-45).[2,4,20] Generally, antidepressants (serotonin and norepinephrine reuptake inhibitors [SNRIs] and selective serotonin reuptake inhibitors [SSRIs]) should be avoided or should be used with

TABLE 2
Clinical Pearls for Primary Care Providers

- Maintain a high index of suspicion for this elusive disease.
- Treatment of bipolar disease generally requires use of more than one drug.
- Do not prescribe SSRIs or SNRIs alone—an antimanic agent must also be used.
- Monitor laboratory values, such as markers of liver, renal, and thyroid function.
- Medication plus psychotherapy yields the best results.
- Risk for suicide is higher among patients with bipolar disorder compared with the general population.
- Never stop long-term medication without discussing this change with a specialist.
- Check for other comorbid conditions that may increase patient's cardiovascular risk.
- More than one psychiatric illness can be present.

an effective antimanic/mood stabilizer. Many patients with severe bipolar symptoms require more than two medications, and it is imperative that all primary care providers understand that often one drug alone is not sufficient treatment for patients with bipolar disorder. For less severe manic

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or hypomanic states, monotherapy with antipsychotics may be effective.

Medications for severe acute manic episodes generally include the mood stabilizers lithium, valproate, or carbamazepine in conjunction with an antipsychotic, such as haloperidol, or an atypical antipsychotic, such as asenapine, aripiprazole, olanzapine, quetiapine, or risperidone.[2] The goal of initial therapy in patients with acute mania is rapid resolution of symptoms and restoration of adequate sleep. Lithium has a slower onset of action than valproate and carbamazepine and requires titration and monitoring. Valproate and carbamazepine have a faster onset of action but are less effective than lithium.[2] Atypical antipsychotics have a more rapid onset of action than mood stabilizers and are effective in controlling acute manic symptoms, psychosis, and sleep disturbances. Patients with severe acute mania may require hospital admission for stabilization, for their safety and the safety of others.

Acute bipolar depressive episodes can be treated with several different medication options, including combination olanzapine and fluoxetine; the atypical antipsychotic quetiapine; and recently lurasidone, alone or in combination with lithium or valproate. Lamotrigine is more effective for maintenance and prevention of depressive episodes than for treatment of acute episodes, and it is also indicated for treatment of bipolar II. Valproate is more effective than lithium for mixed states and can be titrated

more rapidly for faster antimanic effects.[4]

Generally, due to the high rate of recurrence, maintenance medications should be continued indefinitely. Maintenance medications include the mood stabilizers, lamotrigine, and many of the antipsychotics, including olanzapine.[4] Adherence to medications is essential in management of bipolar disorder and can decrease the risk for relapses and destabilization. Poor adherence to medications is common, however, with rates reported at approximately 50%.[21] Patient and family education, as well as psychotherapy, can improve adherence rates.[2] Primary care providers should educate patients and family members about medication options and adverse effects and must stress the need for adherence to prevent relapse. Providers should also understand the safety profile of mood stabilizers and antipsychotics and the required monitoring of laboratory tests for patients on these medications.

Psychosocial treatments are an elemental component of management. Patients should be referred early for psychologic treatments including, but not limited to, family therapy, group therapy, cognitive-behavioral therapy, and psychotherapy, which have been shown to improve daily functioning, recognition of recurrences, and medication adherence.[2] The rate of relapse is significantly lower in patients receiving combination psychotherapy and pharmacotherapy.[22]

Clinical pearls that every primary care provider should know about bipolar disorder are summarized in Table 2 (page 47).

CONCLUSION

Given the substantial impact of bipolar disorder on patients and the community, primary care clinicians must maintain a high index of suspicion for this disorder. An early and accurate diagnosis may reduce the burden of bipolar disorder and improve outcomes. However, diagnosing and treating patients with bipolar disorder is challenging for primary care and specialty clinicians alike. In particular, establishing a diagnosis can be difficult, even for the most seasoned clinician, due to the diversity of symptoms.

Nonetheless, diagnosing bipolar disorder, initiating treatment, and monitoring and referring patients when necessary are certainly within the purview of the primary care provider. **CR**

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