Practical Approaches in the Management of Bipolar Depression: Overcoming Challenges and Avoiding Pitfalls

S4  Pathways to the Diagnosis of Bipolar Disorder
Larry Culpepper, MD, MPH

S10  Bipolar Disorder, Bipolar Depression, and Comorbid Illness
J. Sloan Manning, MD

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Roger S. McIntyre, MD, FRCPC

Cover artwork provided by Anne Therese Naylor, a mental health advocate with bipolar disorder. The Light. Acrylic on Canvas, 11”x15”.
Practical Approaches in the Management of Bipolar Depression: Overcoming Challenges and Avoiding Pitfalls

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TARGET AUDIENCE
This activity has been designed to meet the educational needs of family practice physicians involved in the care of patients with bipolar disorder.

STATEMENT OF NEED/ACTIVITY OVERVIEW
In the past 2 decades, the burden of care for psychiatric complaints in primary care—including bipolar depression—has increased considerably. The prevalence of bipolar disorder (BPD) in primary care has been recently estimated to range up to 4.3%, and in studies with broader definitions of the disorder or in populations with higher-than-usual psychiatric disorders, the prevalence has been reported to be up to 11.4%. Even though BPD is seen commonly in primary care, there are still profound disparities in the delivery of care, including underdiagnosis, misdiagnosis, and inappropriate treatments. In the primary care setting, bipolar depression is often misdiagnosed as unipolar depression. Additionally, patients with BPD have many comorbid psychiatric and medical conditions that often go untreated. The results of a needs assessment survey (N=99) of primary care providers reflected the current literature by demonstrating that BPD is frequently misdiagnosed in the primary care setting, and that medical and psychiatric comorbidities of BPD are often underrecognized and undertreated. There is abundant evidence that BPD can be successfully managed in the primary care setting when adequate physician education, collaborative care teams, and patient education are employed. Efficacious and well-tolerated pharmacologic treatments for BPD are available, and evidence-based pharmacotherapy can be optimally managed by the primary care provider. In this activity, experts in BPD discuss the recognition and management of bipolar depression and associated comorbidities in the primary care setting.

EDUCATIONAL OBJECTIVES
After completing this activity, the participant should be better able to:

- Describe the indicators of bipolar disorder among depressed patients
- Accurately differentiate bipolar depression from unipolar depression
- Implement strategies for the recognition and management of medical comorbidities in patients with bipolar disorder
- Recognize and manage metabolic side effects of agents used in the treatment of bipolar disorder
- Describe strategies for management of common psychiatric comorbidities in patients with bipolar disorder
- Integrate treatment of bipolar depression into primary care practice
- Promote a collaborative care team to manage patients with bipolar depression

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PHYSICIAN CREDIT
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<tr>
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<th>Reported Financial Relationship</th>
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<tr>
<td>Larry Culpepper, MD, MPH</td>
<td><strong>Consulting Fees (eg, Ad boards):</strong> AstraZeneca, Forest Laboratories, Inc., H. Lundbeck A/S, Merck &amp; Co., Inc., Shire plc, Sunovion Pharmaceuticals Inc., Takeda Pharmaceutical Company Limited; <strong>Ownership Interest/Shareholder:</strong> M3 (My Mood Monitor); <strong>Salary:</strong> Physician's Postgraduate Press, Inc.; <strong>Royalty/Patent Holder:</strong> UpToDate®, Oxford University Press</td>
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<td>Lauren Light, PharmD</td>
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**METHOD OF PARTICIPATION**

There are no fees for participating in and receiving credit for this activity. During the period June 2015 through June 2016, participants must (1) read the learning objectives and faculty disclosures, (2) study the educational activity, (3) complete the posttest and evaluation at [http://tinyurl.com/BipolarSuppl](http://tinyurl.com/BipolarSuppl). A statement of credit will be issued only upon completion of an activity evaluation and posttest.

**MEDIA**

Journal supplement

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**FEE INFORMATION**

There is no fee for this educational activity.

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**About the Cover Art**

Anne Therese Naylor is an award-winning writer, artist, advocate, teacher, and mother of 4 children. She has a bachelor’s degree in early childhood education and a master’s degree in special education. Anne Therese began writing creative nonfiction in 1987 after her third child was born and was diagnosed with Down syndrome. In 2001, her short story “The Perfect Mother” was awarded a prize in a national writing competition and published in *Cosmopolitan* magazine. In 2005, an unexpected, intense desire to create artwork was accompanied by the advent of bipolar disorder. Her painting *What Lies Beneath* was awarded first prize in the Central Coast Mental Health Art Works Exhibition in 2008. Her book, *Art from Adversity: A Life with Bipolar*, an account of her experience with bipolar disorder, was published in March 2013. Anne Therese is dedicated to raising awareness, challenging stereotypes, and fighting the stigma of mental illness and disability. *Cover: The Light*. Acrylic on Canvas, 11" x 15".
Primary care physicians (PCPs) serve key roles in first contact and ongoing care for patients with bipolar disorder (BPD). Patients with BPD are commonly encountered by PCPs, given a mean lifetime prevalence of 4.4% for any bipolar disorder. Bipolar disorder is characterized by vulnerability to depression and episodic mania (bipolar I) or hypomania (ie, less severe mania; bipolar II) and, in some cases, rapid cycling between states. Unfortunately, BPD is too frequently misdiagnosed as unipolar depression (major depressive disorder [MDD]). Depending on the population, between 7% and 52% of patients diagnosed with unipolar depression actually have BPD, which may go unrecognized for 10 years or more from symptom onset to first treatment. One study reported that patients were misdiagnosed an average of 3.5 times and had seen 4 physicians before being correctly diagnosed. Thus, there is a substantial need and opportunity to improve the timeliness and accuracy of BPD diagnosis.

Bipolar disorder in primary care
Primary care physicians outnumber psychiatrists 2 to 1 in the United States, and US PCPs provide the majority of mental health care, more than any other specialty. Demand for primary care–based psychiatric services continues to escalate. A 2014 study reported that mental health care, including visits resulting in a BPD diagnosis, increased significantly faster in primary care settings than in psychiatric offices. However, difficulty obtaining specialty consultations may limit PCPs’ capacity to manage patients with BPD effectively. A 2009 survey of approximately 6600 non-federal PCPs reported that 66.8% were unable to arrange outpatient mental health services.

Clearly, a more unified approach to primary care delivery is needed to serve patients with multiple conditions, particularly patients with BPD. Fortunately, primary care practice is being redesigned to better serve such patients, including through development of the patient-centered medical home. This multidisciplinary, team-based collaborative care model integrates the efforts of mental and behavioral health personnel to provide counseling, psychotherapy, substance abuse and addiction management, and other services needed by many patients with BPD.

The Affordable Care Act (ACA) and the Mental Health Parity and Addiction Equity Act have led to increased coverage and increased demand for coverage. An estimated 62 million people are now obtaining better mental health and substance abuse coverage. In July 2014, the Health Resources and Services Administration (HRSA) began an initiative to prepare for this expected escalation of demand. HRSA awarded $54.6 million in ACA funding to support 221 community health centers across 46 states, Washington, DC, and Puerto Rico to bolster staff and services to serve an additional 450,000 patients. One potential consequence of these developments is that some mental health providers may move to group practices, in part to obtain the practice structure needed to bill for mental health services. However, this move may in turn decrease access to health care in other segments of the community.

Diagnostic and treatment challenges in bipolar disorder
Several reasons may explain the lack of diagnosis and the misdiagnosis of BPD. One survey found that although 28% of patients who were misdiagnosed admitted that they underreported their manic and depressive symptoms, the actual percentage of patients underreporting their symptoms was likely much higher. In addition, 60% of misdiagnosed patients felt that physicians had an inadequate understanding of BPD.

In fact, PCPs acknowledge difficulty in diagnosing BPD. In a 2006 survey evaluating the knowledge, attitudes, and awareness of 102 PCPs, the respondents frequently misiden-
ttified various symptoms required for the diagnosis of BPD, and 46% indicated that they did not have experience recognizing BPD symptoms. The vast majority (94%) of these PCPs said they would use a brief screening instrument if one were available. Many PCPs also express concern about being unfamiliar with appropriate medications and their adverse effects. The National Comorbidity Survey Replication reported that 43.4% of individuals with BPD were treated inappropriately by psychiatrists and 73.1% were treated inappropriately by other medical providers. Inappropriate treatments included administration of an antidepressant without an antimanic agent and antidepressant monotherapy.

In the 2006 survey discussed above, up to one-third of PCPs said that they wished to avoid the complexity of prescribing for BPD patients. More than half considered patients with BPD to be more difficult (60%) and time-consuming (51%) than other patients, and they felt less confident in their ability to manage them (75%). The PCPs also were apt to refer, and two-thirds did so in a timely manner. Overall, a minority of PCPs (6%) prescribed pharmacotherapy. These findings emphasize the need for educational efforts and investment in a more integrated, collaborative partnership between PCPs and psychiatric specialists and allied health personnel, as well as other approaches to improve knowledge, comfort, and skill in managing this complex but treatable condition. Treatment of patients with BPD in primary care settings is feasible, especially given the improved adverse effect profiles of newer psychotropic medications.

**Consequences of misdiagnosis or nondiagnosis**

**Morbidity and mortality**

Misdiagnosis or nondiagnosis of BPD may not only be inconvenient for a patient, but may also have costly and far-reaching consequences. The life expectancy of patients with BPD is 8.5 to 9.0 years shorter than that of the general population. Bipolar disorder may increase the risk of developing chronic medical conditions, through biologic as well as behavioral pathways. Early mortality may result primarily from comorbid medical conditions, which may not be adequately diagnosed or treated over long periods. In particular, serious mental illnesses with psychoses, including BPD, have been shown to be an independent risk factor for cardiovascular disease and diabetes. Furthermore, depressed patients often have decreased motivation to perform self-care behaviors, exacerbating current diseases and allowing others to develop. Many patients have no access to regular health care but instead present for care only at times of crisis. Suicide also contributes to premature death. The Global Burden of Disease Study 2010 reported that suicide was 5.7 times more likely in patients with BPD compared with the general population. Failure to initiate appropriate therapy in patients with BPD has been associated with increased hospital use and suicide attempts.

**Behavioral impairment**

A 2011 study reported an association between the number of previous BPD illness episodes and the response to treatment. For the prevention of relapse, patients with 1 to 5 previous episodes were 40% to 60% more likely to benefit from an atypical antipsychotic than those who had >10 previous episodes (for depression, odds ratio [OR] 0.6; 95% confidence interval [CI] 0.4-0.9; for mania, OR 0.4; 95% CI 0.2-0.6). The greater the number of episodes before beginning an effective therapy, the less likely a patient is to respond to treatment.

Bipolar disorder can result in behavioral issues that lead to interpersonal difficulty, including anger, abrasive communication, distrust and paranoia, and disrupted family, social, and health care (PCP) relationships. These behaviors may isolate the patient from needed support. In addition, if BPD is misdiagnosed as unipolar depression and antidepressant therapy is erroneously prescribed, a state of mania or hypomania may be induced, potentially with rapid cycling. Evidence of antidepressant effectiveness in BPD is weak, and monotherapy with antidepressants is contraindicated. Fewer than half of PCPs are aware that antidepressants can cause potentially deleterious effects. Inappropriate treatment has also been associated with higher hospitalization rates and health care costs.

**Recognizing mania or hypomania**

A history of repeated episodes of mania or hypomania is a hallmark of BPD. However, when presenting in primary care, patients with BPD will predominantly exhibit symptoms of depression. Such depressive symptoms are a shared feature of BPD and unipolar depression. Although patients with bipolar I or bipolar II typically cycle from mania to depression with periods of euthymia interspersed, they do not usually visit PCPs during manic or hypomanic episodes. When they do present for medical attention during these episodes, it is often through the emergency department. After a manic episode has subsided, they may seek care with a PCP because of the consequences of the episode (eg, sexually transmitted disease, follow-up after an accident). The care of these consequences may be the priority, and the opportunity to investigate the underlying psychopathology that led to the problem may be missed.

Patients may focus on the current depressive symptoms and may either not recognize or deny manic symptoms. Patients with BPD spend much more time in the depressive phase of the illness compared with mania/hypomania.
or euthymia; in fact, they spend 30% to 50% of their lives with depressive symptoms.43,44 When symptoms were measured on a weekly basis over a mean of 13 years of follow-up, patients with bipolar I reported depressive symptoms 3 times more often than manic symptoms and 5 times more often than cycling/mixed symptoms.42,43 This same measure for patients with bipolar II is startling: they reported depressive symptoms 39 times more often than hypomanic symptoms and 22 times more frequently than cycling/mixed symptoms.42,43 Furthermore, patients with BPD may experience several depressive episodes and have a diagnosis of MDD well established before they experience their initial manic episode.45

Anxiety is a common comorbid psychiatric feature of BPD. Anxiety presentations can make it difficult to address these patients’ mental health needs because they may be more likely to avoid seeking treatment or to drop out of treatment.46 Patients with BPD may present in primary care settings with concerns diagnosed as anxiety, or as anxious depression, with the underlying BPD not recognized.

Patients frequently hesitate to discuss symptoms they consider embarrassing, especially manic or hypomanic symptoms. Many patients also have little insight into the abnormality of their behaviors during manic or hypomanic episodes and minimize or deny the consequences. As a result, recognizing BPD during usual care in primary care settings is difficult. In fact, only 39% of individuals with bipolar I and bipolar II disorders entered treatment during the year of onset; the median delay to initial treatment was 6 years.47 However, a number of cues and case-finding tools can help PCPs efficiently diagnose patients once BPD is suspected.

### Diagnostic tools for bipolar disorder

Patients considered to be at risk of BPD based on current behaviors or risk factors require clinical evaluation. Since visit duration in primary care settings is nearly universally constrained to about 12 to 15 minutes, validated questionnaires can be useful to facilitate assessment in a timely manner.52 They can also help prevent errors due to clinicians’ memory lapses, thus increasing the likelihood of obtaining accurate information for assessment and confident diagnosis.

Patients can fill out questionnaires before the visit or in the office with support from office staff. Questionnaires can be repeated with new depressive episodes to assess the possibility of an intercurrent manic or hypomanic episode. Because patients may lack insight into their manic behaviors or may not realize the impact of these behaviors on their daily lives, early recognition of these patients’ needs is essential.

### Distinguishing bipolar disorder from unipolar depression

The first task for PCPs seeking to improve outcomes for patients with BPD is to increase the early recognition of those likely to have BPD. Although universal screening is not practical, case finding among patients at increased risk is recommended and may be facilitated by the use of several instruments described in the next section. Several red-flag characteristics can be used to identify patients who need further assessment (TABLE 1).40,42,48 Depressive illness itself conveys significantly increased risk of BPD and should lead to inquiry about mania or hypomania before making a diagnosis of MDD. A 2014 study identified 7 risk factors that differentiated BPD from unipolar depression; 4 of these were identifiable at the onset of illness: cyclothymic temperament, family history, young age (<25 years) at onset, and male sex. Additional cues were ≥4 previous depressive episodes, suicide attempts, and substance abuse.49

### TABLE 1 Characteristics that may differentiate BPD from unipolar depression40,42,48

<table>
<thead>
<tr>
<th>Characteristic</th>
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<tr>
<td>Racing thoughts, pressured speech, flight of ideas, inflated self-esteem, irritability, mood lability</td>
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<td>Ability to function with decreased sleep (eg, 2 to 3 hours)</td>
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<td>Early onset of depressive symptoms (eg, during the teenage and early adult years)</td>
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<td>Family history of BPD, which, even if not overtly diagnosed, may be marked by a history of unpredictable behavior and a complicated life (eg, multiple jobs, marriages, relocations, bankruptcies) in first-degree relatives</td>
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<tr>
<td>Risky behaviors; excessive involvement in pleasurable activities</td>
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<tr>
<td>Hypersomnia, motor retardation, and suboptimal work functioning</td>
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<td>Paradoxical response to antidepressants, such as mania or hypomania</td>
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<td>Treatment-resistant depression</td>
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Abbreviation: BPD, bipolar disorder.
functioning and on others, having a family member complete the same instrument (with the patient’s permission) can be helpful in recognizing mania. Such involvement also may open discussion about the condition and help the family to help the patient.

Three instruments have proven useful in the process of diagnosing BPD: the Mood Disorder Questionnaire (MDQ), the Composite International Diagnostic Interview (CIDI), and the My Mood Monitor (M3) test, which can be incorporated into the electronic health record.

**Mood Disorder Questionnaire**
The MDQ is a brief self-report inventory used as a case-finding instrument. The first question has 13 parts, the second question asks about clustering of symptoms, and an additional question assesses the degree of problematic consequences resulting from the reported behaviors. It usually takes only 5 minutes for a patient to complete the questionnaire. Seven or more “yes” responses suggest BPD. In one study in a primary care practice, an MDQ screening score of 7 or higher yielded a sensitivity of 58% and specificity of 93% for detecting BPD compared with structured clinical interview. Although the MDQ can be a helpful instrument, it is not considered a definitive diagnostic measure and further evaluation is required, including in patients for whom the PCP has a high suspicion but the MDQ is not positive. The MDQ is available at http://www.integration.samhsa.gov/images/res/MDQ.pdf.

**Composite International Diagnostic Interview**
The CIDI version 3.0 is a clinician-administered instrument that takes roughly 3 minutes to complete. If positive answers are obtained to 2 “stem” and 1 screening question, 9 further questions are asked that identify manic symptoms. As the number of questions answered in the affirmative increases, so too does the likelihood of a positive BPD diagnosis. For example, if 7 or more items are endorsed, the individual is at high risk (>50%) of having BPD. The CIDI 3.0 was found to detect 67% to 96% of true BPD cases in a population-based at high risk (>50%) of having BPD. The CIDI version 3.0 is particularly valuable because it specifically asks about symptoms constituting the diagnostic criteria. Primary care physicians should inquire about comorbidities such as PTSD or an anxiety disorder, determine the degree and realms of functional impairment, and look for other consequences of disorder-related behaviors. Understanding the severity of symptoms and impairment is the key to differentiating bipolar I and bipolar II. Similarities and differences between manic and hypomanic episodes are shown in TABLE 2. In addition to confirming the diagnosis, this information is important for selecting treatment, counseling patients, and motivating patients to adhere to clinical recommendations. Getting another viewpoint of the patient’s history from a family member or trusted friend (with the patient’s permission) can be very helpful. Requesting medical records from the patient’s previous PCP(s) may yield clues to diagnosis or nondiagnosis.

**Electronic health records case-finding prompts**
At the practice level, integration into existing systems can increase the routine use of case-finding instruments. In a 2012 study, the CIDI was integrated into an electronic health records system. The CIDI module appeared on the screen automatically during the office visit for any patient with a diagnosis of depression. Across 21 primary care sites, the case-finding tool was used in 47.5% of an intervention group (n = 8355), and 2.5% of patients scored at high or very high risk for BPD. Patients in the intervention group were significantly more likely than comparison patients (n = 8799) to receive a new diagnosis of BPD (1.11% vs 0.36%; P < .01) and a new prescription for BPD medications (1.85% vs 1.19%; P < .01).

**Confirming the diagnosis**
To confirm the diagnosis of BPD, clinicians must evaluate the relevant symptoms cited in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5). Information from one of the case-finding tools can be used to guide this evaluation. The CIDI 3.0 is particularly valuable because it specifically asks about symptoms constituting the diagnostic criteria. Primary care physicians should inquire about comorbidities such as PTSD or an anxiety disorder, determine the degree and realms of functional impairment, and look for other consequences of disorder-related behaviors. Understanding the severity of symptoms and impairment is the key to differentiating bipolar I and bipolar II. Similarities and differences between manic and hypomanic episodes are shown in TABLE 2. In addition to confirming the diagnosis, this information is important for selecting treatment, counseling patients, and motivating patients to adhere to clinical recommendations. Getting another viewpoint of the patient’s history from a family member or trusted friend (with the patient’s permission) can be very helpful. Requesting medical records from the patient’s previous PCP(s) may yield clues to diagnosis or nondiagnosis.

To guide the treatment of depressive episodes, a structured symptom-severity assessment using the M3 or a validated depression screen can be helpful. The initial symptom score can serve as a baseline for comparison with
subsequent scores to quantify the patient’s response to treatment.52

Conclusions
Psychiatric complaints in primary care practice continue to grow more prevalent as patients become better informed about mental illness and behavioral disorders through information campaigns across the range of broadcast and social media. It is incumbent upon PCPs to establish rapport, collect information, correct misinformation, and be prepared to accurately diagnose, initiate treatment, and arrange resources, such as psychiatric consultations. An informed patient assessment can yield the correct diagnosis. Key signs of BPD, including episodes of mania or hypomania, early symptom onset, family history, and unpredictable behavior, help to distinguish BPD from unipolar depression. The MDQ, CIDI, M3, and similar case-finding tools can improve BPD recognition and facilitate timely treatment. New clinical arrangements, such as the patient-centered medical home, may provide additional resources both for diagnosing patients with BPD and engaging them in long-term, integrated care for BPD and medical comorbidities. Primary care physicians are ideally placed to identify BPD, initiate early treatment, encourage sustained treatment, facilitate psychiatric consultations, and manage comorbid conditions to improve the health care and quality of life for these patients.

### TABLE 2 DSM-5 criteria for manic or hypomanic episodes

<table>
<thead>
<tr>
<th>Core mood characteristics</th>
<th>Manic episode</th>
<th>Hypomanic episode</th>
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<tbody>
<tr>
<td>All must be present abnormally and persistently</td>
<td>1. Elevated mood</td>
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<td></td>
<td>2. Expansive or irritable mood</td>
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<td></td>
<td>3. Increased energy or goal-directed activity</td>
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<tr>
<th>Core mood duration</th>
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<tr>
<td>Total duration, days</td>
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<td>Daily duration</td>
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<tr>
<th>Behavioral characteristics</th>
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<td>3 or more must be present during above period (4 if only irritability is present)</td>
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<td>• Inflated self-esteem or grandiosity</td>
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<tr>
<td>• Decreased need for sleep (eg, feels rested after only 3 hours of sleep)</td>
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<td>• More talkative than usual</td>
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<tr>
<td>• Flight of ideas or racing thoughts</td>
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<tr>
<td>• Distractibility</td>
</tr>
<tr>
<td>• Increase in goal-directed activity (social, work, school, or sexual)</td>
</tr>
<tr>
<td>• Excessive risk-taking activities with potential for painful consequences</td>
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<tr>
<th>Severity causes marked functional impairment</th>
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<tr>
<td>Yes</td>
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<th>Psychotic symptoms present?</th>
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<tbody>
<tr>
<td>Yes</td>
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</table>

Abbreviation: DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th ed.

REFERENCES
Bipolar Disorder, Bipolar Depression, and Comorbid Illness

J. Sloan Manning, MD

Substantial need exists for the early recognition and treatment of bipolar disorder (BPD) in primary care. Bipolar disorder is linked to many other conditions, so its public health impact reaches far beyond the presenting episode of either depression or mania alone. It is a severe, recurring, lifelong, potentially lethal multisystem condition complicated by a multitude of known comorbid conditions, including both psychiatric and physical diagnoses. Unfortunately, the vast majority of these comorbidities may go unrecognized and undertreated in clinical practice.

Bipolar disorder is more than a disturbance of affect and mood. The first and most important step is to accurately differentiate BPD from major depression or other comorbid psychiatric conditions by identifying mania or hypomania in a patient’s medical history. Not only must the initial symptoms of BPD be recognized and effectively treated, but prevention of recurrences should be a sustained focus of primary care, the most likely venue for patients to seek psychiatric care.

A 2009 systematic review of the literature from 1959 to 2007 reported that, compared with age- and sex-matched control cases in the general population, patients with BPD have a decreased life expectancy because of chronic medical conditions, the pathophysiology of BPD, and lifestyle. The majority of patients with BPD (60%) suffer from one or more comorbid illnesses. When separated into categories, one or more comorbid chronic medical conditions were found in more than 82% of patients with BPD. In another study, a comorbid psychiatric diagnosis was reported in 57% of patients with BPD, while 30% had more than one current disorder, primarily anxiety and substance use. Associations with comorbid conditions are frequently reported in bipolar populations, but the reciprocal association is rarely reported.

The interaction between comorbid conditions and BPD progression in depressive or first-episode manic symptoms may be mediated at least in part by inflammatory processes, oxidative stress, apoptosis, and genetic susceptibility in the neurologic, cardiovascular, autoimmune, and other systems. We do not yet have discrete biomarkers for BPD, which reinforces the need to improve current methods and accuracy in identifying symptoms, behaviors, histories, and known comorbidities. Unfortunately, many patients with BPD have already accumulated a substantial number of poor prognostic factors for subsequent medical outcomes (eg, childhood traumatic events, family history, early onset of BPD, anxiety disorder, and substance abuse) before being accurately diagnosed with the condition. As a result, primary care physicians (PCPs) must be familiar with the clinical features, risk factors, and defining symptomatology of BPD and recognize the potential advantages of integrating primary care and behavioral health for early recognition and intervention.

Treatment of bipolar disorder as a multisystem disorder

Studies characterize BPD as a multisystem, multidimensional disorder. A major feature of BPD is comorbidity or multimorbidity. Both terms describe the array of co-occurring conditions and modifiable risk factors that may be indirectly related to BPD. If left untreated, patients with BPD who have multiple conditions run the risk of relapses and hospitalizations, which impair symptomatic and functional outcomes and lead to higher direct and indirect costs of care than expected from the individual conditions alone. An integrated, collaborative strategy to address multimorbidity has been called for in BPD, but the health care infrastructure has not yet been fully mobilized.

Aggressive, opportunistic screening for comorbid conditions and appropriate management are needed. For medi-
Comorbidity related to lifestyle factors

A review of a patient’s lifestyle is a significant opportunity to improve the health of all patients, whether at the initial presentation or during follow-up. Several suboptimal lifestyle behaviors and risk factors, including a sedentary lifestyle, tobacco smoking, and obesity, are recognized as being significantly influential in BPD symptom progression and functional impairment. In the 2012 report of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study, BP medical comorbidity was independently associated with smoking and other substance use disorders.

While the foundation of BPD treatment is pharmacotherapy, a healthy diet and physical activity are important whether or not a patient with BPD has underlying cardiovascular risk factors. Education about physical activity/exercise, proper nutrition, and wellness is especially needed for patients with BPD. A 2013 review of physical-activity studies in patients with BPD found that suboptimal physical activity was consistently associated with medical comorbidity, social isolation, poor self-efficacy, and lower educational status. However, in a report on a national sample of Veterans Affairs patients, those with BPD were less likely than patients with schizophrenia or no mental illness to report that their provider discussed any nutrition or exercise topic during their office visit. Perhaps it is not surprising, therefore, that patients with BPD, compared with patients without severe mental illness, were more likely to report that they had gained 10 lb in the prior 6 months, had not engaged in walking or strength training, and had poor dietary habits.

Improvements in exercise time, weight, depressive symptoms, and quality of life were reported in patients with BPD who, over 14 weeks, received twelve 60-minute group education sessions on nutrition/weight loss, exercise, and wellness. Another combined nutrition, exercise, and wellness program of cognitive-behavioral therapy for overweight patients with BPD focused on decreasing sugar intake by minimizing or eliminating foods with a high glycemic index. Improvements in cholesterol, triglycerides, body weight, and depressive symptoms were reported, and the participants’ stamina tripled over the course of 20 weeks. Such programs can provide an effective method of improving physical and psychiatric outcomes when employed as adjunctive support to ongoing primary care.

Comorbidity related to medical conditions

Medical comorbidity has long been considered characteristic of BPD. Although cardiovascular and metabolic issues are the most prevalent in BPD, other body systems should not be overlooked, because neurologic, circadian, and respiratory comorbidities are common. Headache and migraine, sleep disruptions, chronic bronchitis, chronic obstructive pulmonary disease, and asthma have all been reported in patients with BPD more frequently than in individuals without BPD. The FIGURE depicts the rates of a number of general medical conditions reported in patients with BPD from 2 different prevalence studies.

Cardiovascular risk factors: Diabetes, obesity, and metabolic syndrome

A meta-analysis showed that 37% of patients with BPD had metabolic syndrome, a proportion twice that of the general population. Recent studies have shown that metabolic syndrome is associated with depressive symptomology. A review of 17 studies evaluated the mortality rate in patients with BPD compared with matched controls who had other psychiatric illnesses and found cardiovascular diseases to be the most frequent cause of excess mortality. When compared with the general US population, patients with BPD and other severe mental illnesses have 1.5 to 2 times the prevalence of dyslipidemia, hypertension, and obesity and up to 3 times the prevalence of diabetes mellitus. Screening for traditional cardiovascular risk factors is warranted in patients with BPD because these risk factors are readily identifiable with established screening approaches and are modifiable.
FIGURE General medical conditions commonly associated with bipolar disorder\textsuperscript{9,42}

Data from 2 studies published in 2014:
Kemp et al\textsuperscript{9}: N = 264, pooled bipolar I (76.9%) and bipolar II (23.1%)
Forty et al\textsuperscript{42}: N = 1216, lifetime rates of comorbidities in bipolar I (70.4%) and bipolar II (29.6%)

Abbreviation: LOC, loss of consciousness.
In recent years, obesity has been recognized as an important comorbidity with significant prognostic implications for patients with BPD. Estimates indicate that more than two-thirds of patients with BPD are overweight or obese, a nearly identical finding from 2 recent studies in different US populations (68.5% and 69.0%). Rates of obesity, particularly abdominal obesity, are reported to be higher in women with BPD than in men. The synergistic relationship between BPD and obesity is significant for diminished cognitive functioning, greater depressive recurrence, and risk of suicidality.

Management of cardiovascular disease
If cardiovascular risk factors are positively identified, statins may be useful in the treatment of patients with BPD and other psychiatric disorders with these known age-, gender-, and ethnicity-related vulnerabilities. The benefits of statin therapy for primary and secondary prevention have been established. Data suggest that if high LDL-C is not corrected by 3 months of exercise and dietary interventions, a statin could be provided for patients older than 40 years who have a major mental illness, including BPD. After 50 years of age, most patients with BPD who have comorbid diabetes or meet ≥2 criteria for metabolic syndrome should be offered a statin. Further research is needed to establish the benefit of statins in this population for the primary prevention of cardiovascular disease and stroke.

Management of overweight/obesity
In 2013, the American Heart Association, American College of Cardiology, and The Obesity Society updated their joint obesity guidelines for PCPs. The structure of the guidelines, based on high-quality evidence, follows the logic of first identifying candidates for intervention by recognizing risks, then advising patients about the risks of unchecked obesity, and then stressing the benefits of weight loss. Only then does the PCP recommend intervention programs, prescribe pharmacotherapy, or refer for bariatric surgery. According to guidance from the US Food and Drug Administration, pharmacologic therapy is approved for patients with a body mass index ≥30 kg/m², or ≥27 kg/m² if there is an obesity-related comorbidity. As adjuncts to diet and exercise, medications approved for long-term treatment of obesity include orlistat, lorcaserin, phentermine-topiramate, naltrexone-bupropion, and liraglutide. These agents have not been studied specifically in individuals with BPD.

Medications and metabolic disturbances
Certain medications used in the management of BPD are associated with weight gain and/or metabolic side effects. Mood stabilizers and atypical antipsychotics are the major pharmacotherapy classes used for the treatment of BPD. Side effects of mood stabilizers are well documented. Lithium and valproate are associated with moderate weight gain, whereas lamotrigine causes little weight gain. Olanzapine is associated with a higher risk of diabetes, dyslipidemia, and weight gain; quetiapine and risperidone are associated with a moderate risk; and aripiprazole, lurasidone, and ziprasidone are associated with a low risk.

Comorbidity related to psychiatric conditions
Adequate screening for psychiatric comorbidities is necessary because they complicate the diagnosis and treatment of BPD, potentially worsening its course and prognosis. Several psychiatric comorbidities frequently accompany BPD, including substance use, anxiety disorders, impulse control and personality disorders, eating disorders, attention-deficit hyperactivity disorder, and suicidality.

Substance or alcohol use
The prevalence of substance abuse among individuals with BPD is estimated to be 40% to 70%. In a study of patients with BPD and current depression, those with a past or current substance use disorder showed significantly worse functioning and a higher risk of suicide than individuals without such a history. Valproate may have a favorable effect in decreasing the use of alcohol. The second-generation antipsychotic aripiprazole has been shown to reduce drug craving.

Anxiety disorders
Anxiety disorders and BPD may have a close neurologic relationship, but more research is needed to clarify the association and determine optimal treatment. Unfortunately, there are no randomized trials of treatments for comorbid anxiety in patients with BPD, and a review showed that lithium mono-therapy or anticonvulsants alone were generally not effective. Reductions in anxiety symptomatology associated with BPD or depression may, however, accompany treatment with some atypical antipsychotics and mood stabilizers.

Anxiety disorders include panic disorder, social phobia, obsessive-compulsive disorder (OCD), generalized anxiety disorder (GAD), and post-traumatic stress disorder (PTSD). Comorbid anxiety disorders have been linked to greater illness severity in patients with BPD compared with patients who have BPD but no anxiety disorders. Panic disorder is much more prevalent in patients with bipolar illness than in the general population and is manifest in bipolar mixed states. Obsessive-compulsive disorder is 8 times more prevalent in patients with BPD than in the general population, with a lifetime comorbid rate of 11% to 21%. A 2014 double-
blind, placebo-controlled, randomized clinical trial of topiramate for OCD in patients with BPD reported significantly better efficacy than placebo in ameliorating OCD. Longitudinal studies have shown poor clinical outcomes for patients with both BPD and anxiety, and a correlation has been found between the presence of anxiety symptoms and the duration and severity of depression in patients with BPD. A dose-like effect was seen, with more anxiety symptoms correlating to longer depressive morbidity.

There is limited evidence for pharmacologic treatment of comorbid anxiety disorders. It is recommended that psychotherapeutic approaches be tried first, given the lack of compelling efficacy data. Social phobia, panic symptomatology, and PTSD appear most closely associated with impaired time to recovery. Cognitive-behavioral therapy has been reported to be effective in patients with BPD, specifically in attenuating OCD, GAD, panic disorder, and PTSD.

Antidepressant use for unipolar depression and anxiety

The use of antidepressants (eg, selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors) in combination with mood stabilizers did not show long-term effectiveness of symptomatic benefit in patients with BPD and depression compared with the continued use of mood stabilizers alone. A 2011 meta-analysis also revealed that antidepressants failed to provide a significant clinical response or remission of depressive symptoms in BPD compared with placebo or other standard treatments. Likewise, a meta-analysis performed in 2013 by the International Society for Bipolar Disorders task force reported insufficient evidence of antidepressant effectiveness in combination with mood stabilizers.

Antidepressants, especially venlafaxine and tricyclics, have also been associated with rapid switching to mania or hypomania. Second-generation antipsychotics may offer direct or adjunctive benefits in conjunction with mood stabilizers to protect against bipolar mood switching.

Conclusions

Both medical and psychiatric comorbidities are very common in BPD, and patients should be screened for the detection and management of BPD as well as the conditions themselves. If comorbid conditions are recognized and treated, serious adverse health outcomes may be averted, including substantial morbidity and mortality. Lifestyle interventions are underutilized, and some evidence indicates the efficacy of dietary measures, particularly in tandem with physical activity and wellness programs. Therapies differ with regard to the risk of weight gain, glucose elevation, and dyslipidemia; clinicians should consider metabolic adverse effects in the pharmacologic management of BPD. Anxiety disorders are likely to share similar pathophysiology origins as BPD, and although this relationship requires clarification, it is clear that comorbid anxiety leads to worse outcomes in patients with BPD. Psychotherapeutic approaches to comorbid anxiety disorders are recommended.

Although challenges remain, both medical and psychiatric comorbid conditions in patients with BPD can be successfully detected, treated, and monitored in the primary care setting.

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Evidence-Based Treatment of Bipolar Disorder, Bipolar Depression, and Mixed Features

Roger S. McIntyre, MD, FRCPC

Bipolar disorder (BPD) is commonly encountered in the primary care setting. The high rate of misdiagnosis of BPD highlights the need for timely and accurate diagnosis and initiation of evidence-based treatments to avoid progression of untreated disease.1-5 Timely recognition is often challenging because the early presentation of BPD is nonspecific, involving a confluence of mood, anxiety, and cognitive symptoms, and often manifests at the subthreshold level.3,4,6-8 Establishing an accurate diagnosis and implementing guideline-concordant care offer the opportunity for improved health outcomes in patients with BPD.

Primary care providers (PCPs) are ideally positioned to initiate pharmacologic and psychosocial treatment as part of an integrated, accountable care plan for BPD once a diagnosis has been accurately established.9 When BPD is diagnosed in the primary care setting, optimal pharmacologic and nonpharmacologic treatment is achievable.10-12 Early recognition is important. If BPD progresses untreated, a response to treatment becomes less likely, and more complex therapeutic management is required to achieve sustained improvement.13,14

The goals of BPD treatment are to stabilize symptoms, prevent relapse, and optimize function (TABLE 1).15 Increasingly, BPD is conceptualized as a chronic disease, as evidenced by the enduring subsyndromal symptoms, sleep difficulties, cognitive dysfunction, psychiatric and medical comorbidity, as well as clinically significant mood reactivity. Clinicians planning care pathways for individuals with BPD must anticipate this long-term course.

Pharmacotherapy for bipolar disorder: General principles

Prescribing trends and polypharmacy

Replicated evidence indicates that antidepressant prescription in BPD is common. However, antidepressants are not indicated for patients with BPD because of their lack of proven efficacy in registration trials as well as the possibility of mood destabilization in subsets of individuals with BPD.16 A 2009 study reported that while 71% of patients with BPD were prescribed an atypical antipsychotic and 53% received a mood stabilizer, 30% received an antidepressant.17 The complexity of BPD often invites the need for complex polypharmacy regimens integrated with patient education and psychosocial treatments in an integrated and accountable management plan.17

Number needed to treat and number needed to harm

For any treatment strategy, whether monotherapy or combination therapy, the practitioner must carefully consider efficacy, tolerability, and safety as treatment is tailored for every individual.18-21 The number needed to treat (NNT) and the number needed to harm (NNH) are practical aids for treatment decisions.22-25 The NNT describes the efficacy of a given treatment by quantifying the number of patients who would have to be treated to achieve a single desired outcome, with lower numbers preferred (ie, <10).24 The NNH describes the number of patients exposed who are expected to yield an additional adverse event. A high NNH is desirable, preferably >10.24 TABLE 2 summarizes the NNT and NNH of pharmacologic options for the treatment of bipolar depression and mania.26,27

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**TABLE 1**

<table>
<thead>
<tr>
<th>Pharmacologic Option</th>
<th>NNT</th>
<th>NNH</th>
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<tbody>
<tr>
<td>Lithium</td>
<td></td>
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<tr>
<td>Carbamazepine</td>
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<tr>
<td>Valproate</td>
<td></td>
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<tr>
<td>Quetiapine</td>
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</tbody>
</table>

**TABLE 2**

<table>
<thead>
<tr>
<th>Pharmacologic Option</th>
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<th>NNH</th>
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<td>Lithium</td>
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<tr>
<td>Valproate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
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</tbody>
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Assessing response to treatment

The response to treatment should be a routine assessment priority that may be systematized with the electronic medical record and the use of measurement tools to capture symptoms and functioning from both the patient’s and provider’s perspectives. The Young Mania Rating Scale and the Montgomery-Asberg Depression Rating Scale are widely used clinician-rated scales for assessing symptom severity.28,29

Several factors may influence the likelihood of responding to treatment, including (but not limited to) the type of illness (bipolar I or bipolar II), number of prior episodes, existence of comorbidity, and phase as well as stage of treatment. For example, patients with 1 to 5 prior depression episodes are 60% more likely to respond to treatment compared with patients with >10 previous episodes (odds ratio [OR] 1.6; 95% confidence interval [CI] 1.02-2.40).2

When formulating the overall treatment strategy, the PCP should anticipate the multidimensionality of the illness and assess comorbidity before initiating any treatment.

Monotherapy treatment in bipolar disorder

Reviewing the extant literature for monotherapy in BPD is beyond the scope of this article. Nevertheless, clinicians should aim to use monotherapy whenever feasible to reduce the potential for medicine-related complications (including adverse effects and drug-drug interactions) and be cautious when considering combination therapy.30 A 2012 study found that monotherapy was associated with fewer adverse effects and lower discontinuation rates compared with combination therapy.31 Efficacy of monotherapy for acute bipolar depression has been demonstrated in a meta-analysis for olanzapine-fluoxetine combination (OFC), quetiapine, and lurasidone.32 For relapse prevention, lithium monotherapy has been reported to be superior to divalproex monotherapy.32 Lamotrigine is approved by the Food and Drug Administration (FDA) for BPD maintenance treatment as monotherapy.26 There is inadequate research supporting the use of antidepressant monotherapy in acute BPD depression, and it is generally discouraged in the treatment of BPD as it can lead to switching to mania.33,34

Combination therapy in bipolar disorder

The following is a brief review of key elements in combination therapy for BPD. Combination therapy may be necessary when monotherapy is insufficient to fully treat acute and breakthrough episodes during maintenance. A meta-analysis of combination therapy concluded that an antipsychotic plus lithium is superior to lithium monotherapy for acute mania.35 For relapse prevention, lithium plus divalproex has also been shown to be superior to divalproex monotherapy.32 A placebo-controlled trial demonstrated that quetiapine plus lithium or divalproex was superior to a mood stabilizer alone for prevention of manic and depressive recurrences regardless of the type of index episode.36 Separate randomized clinical trials of the combination of ziprasidone or olanzapine plus a mood stabilizer compared to a mood stabilizer alone demonstrated a relapse rate in favor of the combination.37,38 Treatment with lurasidone adjunctive to lithium or divalproex significantly improved depressive symptoms compared with a mood stabilizer alone.39

Adverse effects, tolerability, and adherence

A timely and accurate diagnosis, followed by initiation of pharmacotherapy, is the foundation of treatment for BPD. It is important to identify treatments that are well tolerated and likely to be accepted so that patients with BPD will adhere to the treatment for optimal outcomes.40 Adverse effects of mood stabilizers and/or various atypical antipsychotic agents have been reported in specific domains, including antihistaminergic (sedation, weight gain), anticholiner-

### TABLE 1 Goals of treatment for bipolar disorder15

<table>
<thead>
<tr>
<th>Goal</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stabilize</td>
<td>The primary goal is stabilizing mood disturbance</td>
</tr>
<tr>
<td></td>
<td>• Mania and/or</td>
</tr>
<tr>
<td></td>
<td>• Depression</td>
</tr>
<tr>
<td>Prevent</td>
<td>Once stability is achieved, relapse prevention is the goal</td>
</tr>
<tr>
<td></td>
<td>• Encourage adherence and proactivity, including patients’ symptom tracking</td>
</tr>
<tr>
<td></td>
<td>• Mobilize family and social support</td>
</tr>
<tr>
<td>Maximize function</td>
<td>Maximize function (family, social, work) over the long term</td>
</tr>
<tr>
<td></td>
<td>• Reassess treatment goals</td>
</tr>
<tr>
<td></td>
<td>• Mobilize nonpharmacologic therapies to address dysfunctional cognitive and behavioral patterns</td>
</tr>
</tbody>
</table>
**EVIDENCE-BASED TREATMENT**

**TABLE 2** Pharmacologic treatment options for bipolar disorder

<table>
<thead>
<tr>
<th>Agent</th>
<th>Starting dose</th>
<th>Target dose</th>
<th>NNT</th>
<th>NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute depression</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lurasidone</td>
<td>20 mg once daily</td>
<td>20 to 120 mg once daily</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>Olanzapine-fluoxetine (OFC)</td>
<td>3 mg/25 mg to 6 mg/25 mg once daily in the evening</td>
<td>6 mg/25 mg to 12 mg/50 mg</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>50 mg once daily at bedtime</td>
<td>300 mg once daily at bedtime</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td><strong>Acute mania</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>200 mg twice daily</td>
<td>200 mg once daily to 800 mg twice daily</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Divalproex</td>
<td>IR: 750 mg daily in divided doses ER: 25 mg/kg once daily</td>
<td>IR: 60 mg/kg daily ER: 60 mg/kg daily</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Lithium*</td>
<td>300 to 900 mg 1 to 2 times daily; titrate to serum level of 0.6 to 1.5 mEq/L</td>
<td>900 to 1800 mg per day</td>
<td>4</td>
<td>27</td>
</tr>
<tr>
<td>Aripiprazole*</td>
<td>10 to 15 mg once daily if adjunctive therapy 15 mg once daily if monotherapy</td>
<td>15 to 30 mg once daily</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Asenapine</td>
<td>5 mg sublingual twice daily if adjunctive therapy 10 mg sublingual twice daily if monotherapy</td>
<td>10 mg sublingual twice daily</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Olanzapine*</td>
<td>10 mg once daily if adjunctive therapy 10 to 15 mg once daily if monotherapy</td>
<td>5 to 20 mg once daily</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Quetiapine*</td>
<td>XR: 300 mg once daily IR: 50 mg twice daily</td>
<td>400 to 800 mg per day (XR once daily or IR twice daily)</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Risperidone</td>
<td>2 to 3 mg/day</td>
<td>1 to 6 mg per day</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Ziprasidone*</td>
<td>40 mg twice daily</td>
<td>40 to 80 mg twice daily</td>
<td>7</td>
<td>5</td>
</tr>
</tbody>
</table>

ER, extended release; IR, immediate release; NNH, number needed to harm for specific adverse effect compared with placebo (higher is better); NNT, number needed to treat for response compared with placebo (lower is better); XR, extended release.

*Approved for bipolar maintenance; quetiapine (XR and IR) and ziprasidone are approved for maintenance only as adjunctive therapy.

Gic (dry mouth, constipation), alpha-1 blockade (dizziness, orthostasis), dopamine antagonism (hyperprolactinemia, psychomotor slowing, extrapyramidal symptoms [EPS]), and increased serotoninergic effect (sexual dysfunction). Time to recurrence of depressive episodes has been reported to be significantly shorter in obese versus nonobese patients, so weight-loss measures are advised in these patients, as is the consideration of using BPD pharmacotherapies known to have fewer metabolic side effects.

**Features of BPD that influence treatment decisions**

**Cognition**

Bipolar disorder is a complex disorder that usually presents with one or more comorbid conditions. Altered cognition, impaired attention, difficulties with communication, and related behavior patterns can be barriers to a patient’s interaction with the health care system and may affect both readiness for treatment and adherence, and ultimately affect the quality of treatment. Cognitive impairment has also been found to be associated with some comorbid conditions. For instance, a 2012 study of BPD patients found greater cognitive impairment in overweight or obese patients (body mass index [BMI] ≥25.0 kg/m²; n = 48) compared with normal-weight patients (BMI 18.5 to 24.9 kg/m²; n = 19), particularly in the domains of attention, psychomotor processing, and overall verbal fluency. In addition, a meta-analysis reported that patients with bipolar II had significantly lower cognitive performance than healthy controls and at nearly the same severity as bipolar I.

**Mixed features**

One of the more heterogeneous clinical presentations of BPD is the phenomenon of mixed mood states. Mixed states or mixed
features are conceptualized as the co-occurrence of manic and depressive symptoms. Mixed features during a depressive episode appear to be very common. For example, in a study of 1380 patients experiencing an index episode of bipolar depression, 54% had subsyndromal mania. The recent designation of mixed features in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) recognizes subsyndromal depressive symptoms while manic, or subsyndromal manic symptoms while depressed. For example, a patient with mixed features can meet the full criteria for a manic episode and have only a minimum of 3 of the symptoms of a major depressive episode. Conversely, he or she may meet all the criteria for major depressive disorder and have 3 or more of the symptoms of mania or hypomania.

Patients with a mixed presentation may have a suboptimal response to pharmacotherapy compared with those presenting with a manic or depressive episode, and these patients have an increased risk of subsequent affective episodes. The principal challenge of treating these patients is to simultaneously address both manic and depressive symptoms. There are currently no evidence-based guidelines to specifically address the treatment of patients falling into the category of DSM-defined mixed features. For patients with mixed symptoms during mania, atypical antipsychotics and divalproex are effective. The evidence base is larger for the use of atypical antipsychotics in mixed states, for which they have demonstrated mitigation of manic and depressive symptoms. Divalproex also is capable of mitigating manic/hypomanic as well as depressive symptoms in adults with mixed mania and mixed hypomania. However, there is an absence of replicated evidence documenting antidepressant effects with divalproex in large placebo-controlled trials. Patients with BPD and mixed features should not be treated with antidepressant monotherapy because of a risk of greater mania severity or switching to mania.

Pharmacologic treatment options
The following provides a brief summary of the pharmacologic agents used in the treatment of BPD.

Antidepressants
No antidepressant is FDA approved for BPD as monotherapy. Of note, fluoxetine in combination with olanzapine is approved. Antidepressants are used in up to 30% of bipolar treatment regimens, as reported by the SDI/Verispan's Prescription Drug and Diagnosis Audit prescribing database from 3100 office-based US physicians across 29 specialties. Antidepressants are problematic in the treatment of BPD depression because of their lack of efficacy and variability of outcomes, including multiple medication treatment failures and treatment resistance. A meta-analysis reported that augmentation with an antidepressant does not improve response rates or remissions beyond the effects of mood stabilizers alone.

The risk-benefit profile for the use of antidepressant medications in patients with BPD is controversial. The International Society for Bipolar Disorders evaluated the evidence base for efficacy and safety of antidepressant medications in BPD. The society concluded that there was insufficient evidence to endorse the use of antidepressants, but acknowledged that individual patients may benefit from antidepressants. Selective serotonin reuptake inhibitors and bupropion may be less likely to induce manic switching than tricyclic/tetracyclic antidepressants or serotonin-norepinephrine reuptake inhibitors.

Mood stabilizers and anticonvulsants
Lithium and selected anticonvulsants are possible therapeutic options for the treatment of BPD, but lithium and anticonvulsants are not approved for bipolar depression. Lamotrigine is approved as maintenance therapy for the prevention of mood episodes (mania, depression, hypomania, and mixed episodes).

Lithium. Lithium is an important pharmacotherapy for regulation of mood in patients with BPD and it decreases the risk of suicide in these patients. The antisuicide effect of lithium is purported to act in part by decreasing aggression and impulsivity. Lithium is approved for mania and for maintenance only (not for mixed features). Both lithium monotherapy and lithium plus divalproex in combination have been shown to be more effective than divalproex monotherapy to prevent BPD relapse. Common and mild adverse effects include tremor, fatigue, lethargy, dry mouth, dehydration, polyuria, weight gain, and gastrointestinal effects.

Divalproex. Divalproex is approved for the treatment of mania only and is not approved for mixed features or maintenance treatment. Divalproex plus lamotrigine was found to be superior to lamotrigine monotherapy for depressive symptoms. For prevention of relapse, divalproex plus lithium achieved a sustained benefit lasting up to 2 years as compared with divalproex monotherapy (hazard ratio 0.59; 95% CI 0.42-0.83; P=.0023). Adjunctive use of divalproex with an atypical antipsychotic may be effective for depression in some patients. Common adverse effects include nausea, weight gain, and, less commonly, metabolic and menstrual irregularities. Because of the risk of neural tube defects and other teratogenic effects, women of childbearing potential should use divalproex only when essential.

Lamotrigine. Lamotrigine is approved for BPD maintenance only and is not approved for acute mania or depression. Two randomized controlled trials indicated that
lamotrigine was superior to placebo in the maintenance and prevention of depressive symptoms in patients with BPD.\textsuperscript{58,60} In double-blind, placebo-controlled studies of acute bipolar depression, however, lamotrigine showed inadequate efficacy as demonstrated by a double-digit NNT (eg, >10).\textsuperscript{70,71} Common and mild adverse effects of lamotrigine include headache, fatigue, ataxia, skin rash, nausea, and vomiting, and limited evidence suggests that it could contribute to weight loss.\textsuperscript{61}

**Carbamazepine.** Carbamazepine is approved for acute mania or mixed episodes, but not for BPD maintenance. Carbamazepine has been found to be more effective in patients with nonclassic features such as mood-incongruent delusions, which may suggest a broader spectrum of activity.\textsuperscript{72,73} For the first 6 months of a 2003 trial in untreated patients with BPD, carbamazepine was narrowly more effective than lithium in preventing relapses, although at 2 years significance shifted in favor of lithium over carbamazepine.\textsuperscript{74} More recently, 2 double-blind, randomized, placebo-controlled trials showed that carbamazepine extended-release capsules were efficacious in the treatment of acute mania in patients experiencing mania or mixed episodes.\textsuperscript{75,76} Common and mild adverse effects include drowsiness, headache, anxiety, memory problems, diarrhea, constipation, heartburn, and dry mouth. As do many other anticonvulsants, carbamazepine has teratogenic effects.\textsuperscript{77}

**Atypical antipsychotics**

Atypical antipsychotics are effective for BPD in the manic/hypomanic, depressive, and maintenance phases, but only 3 have been FDA approved for bipolar depression. The approved agents differ markedly in terms of tolerability and safety. Certain antipsychotics have a propensity for metabolic disruption, including weight gain. All 3 antipsychotics that are FDA approved for bipolar depression (olanzapine-fluoxetine, quetiapine, and lurasidone) have reasonably low NNT values, as determined from randomized, placebo-controlled trials and meta-analyses (TABLE 2).\textsuperscript{23,38,77} Atypical antipsychotics approved for bipolar depression are comparable in terms of NNT (efficacy) but differ in terms of NNH (tolerability).\textsuperscript{26,27} A number of atypical antipsychotics have also been approved for acute mania as monotherapy or adjunctive treatment (TABLE 2).

**Olanzapine-fluoxetine.** OFC has been FDA approved for bipolar depression based on replicated placebo-controlled studies.\textsuperscript{78-80} A long-term follow-up trial in 2009 reported superiority of OFC to lamotrigine for both depressive and manic symptoms.\textsuperscript{79} Common adverse effects include sedation, hypersomnolence, and weight gain (NNH = 6) and, less commonly, a risk of EPS.\textsuperscript{27} In a systematic review of randomized trials, olanzapine was associated with a mean weight gain of 5.0 kg.\textsuperscript{81}

**Quetiapine.** Quetiapine monotherapy was approved after demonstrating efficacy in acute bipolar depression, as supported by several large randomized trials of the immediate-release formulation and the extended-release formulation.\textsuperscript{82-86} Common adverse effects associated with quetiapine are sedation (NNH = 5), weight gain, and, less commonly, EPS.\textsuperscript{27}

**Lurasidone.** Lurasidone was FDA approved in 2013 as monotherapy or as an adjunct to lithium or divalproex for patients with bipolar depression. Evidence of efficacy was supported in 2 randomized clinical trials, 1 for adjunctive therapy\textsuperscript{87} and a 6-week monotherapy trial.\textsuperscript{39,87} Adverse effects of lurasidone include nausea, somnolence, tremor, akathisia (NNH = 15), and insomnia.\textsuperscript{25} Metabolic adverse effects have been reported to be minimal in terms of weight gain, lipid abnormalities, and measures of glycemic control.\textsuperscript{44,88}

**Nonpharmacologic treatments**

Nonpharmacologic interventions consisting of both psychosocial and lifestyle strategies should be integrated into the overall treatment of bipolar depression. Psychosocial interventions that have been used successfully in bipolar depression as adjuncts to pharmacotherapy include cognitive-behavioral therapy, patient education, and family-focused therapies.\textsuperscript{89-95} Some evidence shows that these interventions are associated with greater symptom stability, fewer relapses, and longer time to relapse.\textsuperscript{96} Multidimensional, collaborative, and measurement-based care improves health outcomes for patients with BPD.\textsuperscript{96,97,101} Referral to a psychiatrist, psychologist, psychotherapist, or social worker can provide the patient a full range of psychological therapy if needed, but initial and ongoing patient education efforts can occur at the PCP visit, thereby reinforcing prior and subsequent psychiatric care and psychosocial support.\textsuperscript{102,103} Primary care providers may have different roles depending on the practice setting (eg, primary care medical homes may be integrated with psychiatric support as opposed to independent practices). They should attempt to engage in a partnership with sources of psychiatric care to aid in the monitoring of symptoms and the long-term management of medical comorbidities.

Primary care providers should promote lifestyle management for patients with BPD, focusing on exercise and wellness, particularly for patients at increased cardiometabolic risk.\textsuperscript{40,104-106} Studies suggest that physical activity yields neurocognitive benefits, including an antidepressant and anxiolytic effect.\textsuperscript{107-109} Lack of physical activity in patients with BPD is pervasive and can have negative effects.
Conclusions

Bipolar depression is frequently encountered in the primary care setting. Timely and accurate diagnosis and appropriate treatment, informed by FDA-approved treatments, can have a substantial impact for the patient with BPD. Treatment selection for acute symptomatic management should anticipate the long-term course of the illness. Against this background, consideration of both short-term and long-term adverse events is essential.

Mood stabilizers and atypical antipsychotics should be considered as the primary evidence-based treatment choices because of demonstrated efficacy and tolerability. Antidepressant monotherapy should be avoided wherever possible because of lack of efficacy in bipolar depression and the increased risk of triggering manic symptoms. OCF, quetiapine, and lurasidone are indicated for bipolar depression and have single-digit NNTs. Metabolic adverse effects and clinical weight gain have been documented with some atypical antipsychotics as shown by a low NNH, and these effects may be a concern for some patients. Whenever possible, patient education interventions should be integrated into the treatment paradigm.

Bipolar disorder can be a debilitating condition, and delayed recognition and treatment can have adverse clinical, functional, and economic outcomes. The PCP can prevent the unnecessary prolongation of BPD symptoms through prompt diagnosis and management of patients with this recognizable and treatable disorder.

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