## **REVIEW ARTICLE**

# The Diagnosis and Treatment of Bipolar Disorder: Decision-Making in Primary Care

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## ABSTRACT

Bipolar disorder is a chronic episodic illness, characterized by recurrent episodes of manic or depressive symptoms. Patients with bipolar disorder frequently present first to primary care, but the diversity of the potential symptoms and a low index of suspicion among physicians can lead to misdiagnosis in many patients. Frequently, co-occurring psychiatric and medical conditions further complicate the differential diagnosis. A thorough diagnostic evaluation at clinical interview, combined with supportive case-finding tools, is essential to reach an accurate diagnosis. When treating bipolar patients, the primary care physician has an integral role in coordinating the multidisciplinary network. Pharmacologic treatment underpins both short- and long-term management of bipolar disorder. Maintenance treatment to prevent relapse is frequently founded on the same pharmacologic approaches that were effective in treating the acute symptoms. Regardless of the treatment approach that is selected, monitoring over the long term is essential to ensure continued symptom relief, functioning, safety, adherence, and general medical health. This article describes key decisionmaking steps in the management of bipolar disorder from the primary care perspective: from initial clinical suspicion to confirmation of the diagnosis to decision-making in acute and longer-term management and the importance of patient monitoring.

Prim Care Companion CNS Disord 2014;16(3):doi:10.4088/PCC.13r01609 © Copyright 2014 Physicians Postgraduate Press, Inc.

Submitted: November 14, 2013; accepted January 27, 2014. Published online: June 19, 2014. Corresponding author: Larry Culpepper, MD, MPH, Department of Family Medicine, Boston University Medical Center, 1 BMC PI, Dowling 5, Boston, MA 02118 (laculpep@bu.edu). **P**rimary care physicians are the first point of contact for many patients with bipolar disorder, and they have a fundamental role in the diagnosis and treatment of this lifelong condition.<sup>1</sup> The diversity of the potential symptoms in bipolar disorder may mean that the condition will remain unrecognized in many patients for several years. Making an inaccurate diagnosis—often of major depressive disorder (MDD)—also may be problematic, as it leads potentially to initiation of inappropriate treatment and a deterioration in symptoms.

Bipolar disorder is a chronic illness that is typically experienced first in early adulthood, although onset in childhood or in older age may also occur. Bipolar disorder can be divided into subtypes, including bipolar I and bipolar II disorder. Bipolar I disorder is distinguished by full-blown manic episodes that are more impairing than the hypomanic episodes that characterize bipolar II disorder. Depression, which is the presenting symptom of bipolar disorder in most patients, may impose a greater disease burden, in terms of both duration and impact, than manic symptoms. Depressive symptoms may be of similar severity in bipolar I and II disorder, and, therefore, bipolar II disorder should not be considered a "milder" illness than bipolar I. The form of the disease that individuals experience tends to be stable over their lifetime. For patients with either condition, the primary care physician can play an important role, often working with psychiatric consultants, in both managing treatment and monitoring the bipolar disorder and ensuring that other health care needs are met, including preventive care and managing chronic comorbid medical conditions.

Either a manic episode or a depressive episode may be the first presentation of bipolar disorder. The subsequent disease course is characterized by repeated manic or depressive episodes, which are separated by periods during which symptoms do not meet diagnostic criteria.<sup>2</sup> Even during these "euthymic" periods, patients may continue to experience some symptoms and decreased functioning,<sup>3</sup> and brain function continues to be abnormal on functional magnetic resonance imaging (MRI).<sup>4</sup> The timing of the recurrent mood episodes and their polarity (whether manic or depressive), duration, and severity are highly variable between patients and can also vary in the same patient over time. The symptoms typically have a severely debilitating impact on the patient's functioning, employment or educational prospects, and quality of life, and they can substantially elevate the risk of suicide, particularly during depressive episodes with or without mixed features.<sup>2,5-7</sup>

Early, accurate diagnosis can substantially reduce the burden of bipolar disorder and improve the long-term outcome for patients.<sup>8,9</sup> Establishing the diagnosis can, however, be problematic, given the diversity of symptoms that can suggest a number of alternative diagnoses. A high index of suspicion that the symptoms may indicate bipolar disorder is essential.

This review recommends key decision-making steps in the management of patients with bipolar disorder—from the initial stages of clinical suspicion, to confirmation of the diagnosis, through acute and longerterm management and monitoring (Figure 1).

- Patients with bipolar disorder frequently present to primary care, but the diversity of the potential symptoms and a low index of suspicion can lead to misdiagnosis in many patients.
- A thorough diagnostic evaluation at clinical interview, combined with supportive case-finding tools, is essential to reach an accurate diagnosis.
- Pharmacologic treatment underpins both the short- and long-term management of bipolar disorder. Whichever treatment approach is selected, monitoring over the long-term is essential to ensure continued symptom relief, functioning, safety, adherence, and general medical health.

## Table 1. Clinical Decision Steps in Bipolar Diagnosis

- 1. Establish whether the presenting symptoms raise a suspicion of bipolar disorder
- 2. Employ case-finding tools to support the preliminary diagnosis of bipolar disorder
- 3. Conduct a detailed clinical interview that comprehensively covers the patient's medical and family history—together with relevant physical examinations and laboratory tests—to confirm the bipolar diagnosis, identify comorbid medical conditions, and exclude alternative diagnoses

## MAKING THE DIAGNOSIS OF BIPOLAR DISORDER

Decision steps in the diagnosis of bipolar disorder are summarized in Table 1.

## When to Suspect Bipolar Disorder

Patients who first present to primary care with bipolar disorder may show a wide range of mood-related symptoms, including depression, anxiety, mood swings, irritability, fatigue, difficulty in sleeping, and inability to focus and concentrate. Certain psychiatric and medical comorbidities are also extremely common and, by their presence, raise a suspicion of bipolar disorder. The patient's social history will often show characteristic sequelae of the illness, such as relationship and marital problems, erratic occupational histories, financial troubles, and recurrent legal issues.

Diagnosing bipolar disorder in the face of the diverse symptoms and sequelae is a challenge that requires a high index of suspicion.

*Suspicion of a manic episode.* A full-blown manic episode that includes the cardinal symptoms may be readily identifiable in most patients with bipolar I disorder, but the symptomatology can be variable (Table 2). Particular attention should be paid to the symptomatology of mania in patients with comorbidities (eg, anxiety, panic disorder, substance abuse), as these symptoms can further complicate or mask the diagnosis. Patients experiencing a manic episode should receive urgent specialist investigation and treatment because of the high risk of harm to self or others. Manic episodes frequently require intensive outpatient treatment or admission to a psychiatric facility (including involuntary

## Figure 1. Decision-Making Steps in Bipolar Disorder Diagnosis and Management



admission) to provide a safe environment during treatment induction.

Milder episodes of mania, such as hypomania, which is characteristic of bipolar II disorder, are more easily missed. For many patients, a hypomanic episode represents a period of "wellness" after an episode of depression, and they may not report hypomanic symptoms unless specifically questioned. These patients may even challenge their bipolar diagnosis. The provision of information in the form of written materials, recommended Web sites, and support group details can help these patients to accept their diagnosis.

*Suspicion of a depressive episode.* Depressive symptoms are experienced most frequently and for the longest duration in bipolar disorder, and are the most common reason for patients to seek care (Figure 1).<sup>10–12</sup>

The symptoms of depression in bipolar disorder closely resemble those in MDD,<sup>5,13</sup> and, so, it is recommended that every patient presenting with depression should be evaluated for bipolar disorder (Table 3). Patient characteristics that can help to differentiate bipolar depression and MDD are included below and in Figure 2.<sup>14-16</sup>

 A history of mania or hypomania. This is the major differentiator of bipolar disorder from MDD (mania in bipolar I and hypomania in bipolar II disorder). All patients with depression should be questioned about current or prior manic or hypomanic symptoms (see Table 2). As discussed later, use of a

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## Table 2. Manic and Hypomanic Episodes: DSM-5 Criteria<sup>a</sup>

## Manic Episode

Criteria A-D constitute a manic episode

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting at least 1 week and present most of the day, nearly every day (or any duration if hospitalization is necessary)

Note: In DSM-5 versus DSM-IV, Criterion A is revised to include increased energy/activity as a core symptom

B. During the period of mood disturbance and increased energy or activity, 3 (or more) of the following symptoms (4 if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior:

- (1) Inflated self-esteem or grandiosity
- (2) Decreased need for sleep (eg, feels rested after only 3 hours of sleep)
- (3) More talkative than usual or pressure to keep talking
- (4) Flight of ideas or subjective experience that thoughts are racing
- (5) Distractibility (ie, attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed
- (6) Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (ie, purposeless non-goal-directed activity)
- (7) Excessive involvement in activities that have a high potential for painful consequences (eg, engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)
- C. The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features
- D. The episode is not attributable to the physiologic effects of a substance (eg, a drug of abuse, a medication, other treatment) or to another medication At least 1 lifetime manic episode is required for a diagnosis of bipolar I disorder

## Hypomanic Episode

Criteria A-F constitute a hypomanic episode

- A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting at least 4 consecutive days and present most of the day, nearly every day
- B. During the period of mood disturbance and increased energy and activity, 3 (or more) of the following symptoms (4 if the mood is only irritable) have persisted, represent a noticeable change from usual behavior, and have been present to a significant degree:
  - (1) Inflated self-esteem or grandiosity
  - (2) Decreased need for sleep (eg, feels rested after only 3 hours of sleep)
  - (3) More talkative than usual or pressure to keep talking
  - (4) Flight of ideas or subjective experience that thoughts are racing
  - (5) Distractibility (ie, attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed
  - (6) Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
  - (7) Excessive involvement in activities that have a high potential for painful consequences (eg, engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)
- C. The episode is associated with an unequivocal change in functioning that is uncharacteristic of the individual when not symptomatic
- D. The disturbance in mood and the change in functioning are observable by others
- E. The episode is not severe enough to cause marked impairment in social or occupational functioning or to necessitate hospitalization. If there are psychotic symptoms, the episode is, by definition, manic

F. The episode is not attributable to the physiologic effects of a substance (eg, a drug of abuse, a medication, other treatment) or to another medication Hypomanic episodes are common in bipolar I disorder but are not required for a diagnosis of bipolar I disorder. Criteria for a past or current hypomanic episode and a past or current major depressive episode are required for diagnosis of bipolar II disorder

<sup>a</sup>Reprinted with permission from American Psychiatric Association.<sup>5</sup>

bipolar screening tool in all patients diagnosed with a major depressive episode may represent a timeefficient practice routine as a first step, followed by a confirmatory clinical interview guided by the responses.

- (2) Age at onset. The age at onset for bipolar depression is typically earlier than for MDD, with first symptoms often manifesting between the ages of 13 and 18 years.<sup>17</sup> By contrast, the symptoms of MDD first manifest, on average, in the mid- to late 20s.<sup>18</sup>
- (3) Atypical features. Patients with bipolar disorder more often experience "atypical" features of depression, such as hypersomnia, hyperphagia, and rejection sensitivity, when compared with MDD. Mood lability, psychotic symptoms, psychomotor retardation, and pathological guilt are also more predictive of bipolar disorder.
- (4) Course of illness. Bipolar disorder is characterized by more frequent and more rapid onset of recurrences than MDD. A history of frequently

recurring depression, especially with melancholic or psychotic features, may be an indicator of bipolar disorder.

- (5) Treatment history. A history of lack of response to antidepressants may point to a bipolar diagnosis. Antidepressant monotherapy may also increase the risk of rapidly "switching" a bipolar patient from a depressive to a manic episode.<sup>19</sup>
- (6) Family history. A history of mood disorders in the family is a strong predictor for bipolar disorder.

*Suspicion of mixed features.* "Mixed features" is a new specifier in the *DSM-5*, which is added in place of "mixed episodes" in the *DSM-IV-TR*. Patients with concurrent manic and depressive symptoms may experience significant energy, impulsivity, and irritability in combination with depression and hopelessness.<sup>5,20</sup> The presence of mixed states is a particular danger to patients, because the combination of dysphoria, high energy, and decreased sleep places them at high risk for suicide.<sup>21</sup>

## Table 3. Major Depressive Episode: DSM-5 Criteriaª

#### Criteria A-C Constitute a Major Depressive Episode

Note: the DSM-5 diagnostic criteria are the same for major depressive disorder and for depressive episodes of bipolar disorder

- A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from the previous functioning; at least 1 of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure
  - (1) Depressed mood most of the day, nearly every day, as indicated by either subjective report (eg, feels sad, empty, or hopeless) or observation made by others (eg, appears tearful) (Note: in children and adolescents, can be irritable mood)

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

- (3) Significant weight loss when not dieting or weight gain (eg, a change of more than 5% of body weight in a month) or decrease or increase in appetite nearly every day
- (4) Insomnia or hypersomnia nearly every day
- (5) Psychomotor agitation or retardation nearly every day (observable by others; not merely subjective feelings of restlessness or being slowed down)
- (6) Fatigue or loss of energy nearly every day
- (7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
- (8) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
- (9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicidal attempt or a specific plan for committing suicide
- B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
- C. Episode is not attributable to the physiologic effects of a substance or to another medication
- Major depressive episodes are common in bipolar disorder, but are not required for a diagnosis of bipolar I disorder. Criteria for a past or current hypomanic episode and a past or current major depressive episode are required for a diagnosis of bipolar II disorder

<sup>a</sup>Reprinted with permission from American Psychiatric Association.<sup>5</sup>

## Figure 2. Key Differentiating Features of Depressive Symptoms in Bipolar Disorder Versus Major Depressive Disorder (MDD)<sup>a</sup>



<sup>a</sup>Based on Manning,<sup>14</sup> McIntyre,<sup>15</sup> and Moreno et al.<sup>16</sup>

The *DSM-5* includes minimum duration criteria for bipolar I (7 days) and bipolar II (4 days) manic or hypomanic episodes, respectively.<sup>5</sup> These criteria are useful in a research context to identify patients with a high likelihood of these conditions. However, in clinical practice, patients frequently have episodes that do not meet these minimum duration criteria. The *DSM* classification of bipolar disorder not otherwise specified (NOS) may be used in such cases.<sup>5</sup> These criteria are retained in the recently published *DSM*-5, although NOS is changed to "not elsewhere defined." A new bipolar classification proposed by the *DSM-5* is "other specified bipolar and related disorders," which includes individuals with a past history of MDD who meet the criteria for hypomania except for the duration (hypomania requires at least 4 consecutive days of symptoms) or individuals with insufficient hypomanic symptoms to establish a bipolar II diagnosis (although the duration is at least 4 days). The division of bipolar disorder into subtypes is discussed in further detail elsewhere in this article.

## The Role of Case-Finding Tools

Once a suspicion of bipolar disorder is raised, casefinding tools can offer a rapid assessment that helps to differentiate mood disorders (Figure 1). Case-finding tools cannot by themselves establish a bipolar diagnosis but are helpful in combination with the clinical interview (discussed below). A conflicting outcome from a case-finding tool and the interview may justify specialist consultation or referral.

Widely used instruments are the Mood Disorder Questionnaire (MDQ) and the Composite International Diagnostic Interview, version 3.0 (CIDI). The MDQ is a tool, completed by the patient, that includes 13 items to establish the presence of mood disorders and 2 questions to determine the level of functional impairment (Table 4).<sup>22</sup> If the patient endorses 7 or more of the 13 items, confirms that 2 or more symptoms occurred at the same time, and rates the functional impairment as moderate to severe, then the MDQ is considered positive. Many patients with bipolar disorder lack insight into their symptoms, so it can be informative to ask a family member or friend to complete the MDQ on the patient's behalf as well.

The CIDI is a structured interview performed by the physician.<sup>23</sup> A positive answer to 1 of 2 "stem questions" leads to 12 questions that are designed to identify manic symptoms (Table 5).<sup>14,23</sup> The more questions that are answered in the affirmative, the greater the likelihood of a positive diagnosis. As with the MDQ, the CIDI can be performed in a few minutes. Information and training are available on how to apply tools such as the MDQ and CIDI.<sup>24,25</sup> Both tools have been found useful in primary care practice.<sup>14</sup>

| Table 4. The Mood Disorder Questionnaire <sup>a</sup>  |        |
|--|--------|
| Please answer each question to the best of your ability  |        |
| 1. Has there ever been a period of time when you were not your usual self and  |        |
| you felt so good or so hyper that other people thought you were not your normal self or you were so hyper that you got into trouble?   | Yes/No |
| you were so irritable that you shouted at people or started fights or arguments?   | Yes/No |
| you felt much more self-confident than usual?  | Yes/No |
| you got much less sleep than usual and found you didn't really miss it?  | Yes/No |
| you were much more talkative or spoke much faster than usual?  | Yes/No |
| thoughts raced through your head or you couldn't slow your mind down?  | Yes/No |
| you were so easily distracted by things around you that you had trouble concentrating or staying on track?   | Yes/No |
| you had much more energy than usual?   | Yes/No |
| you were much more active or did many more things than usual?  | Yes/No |
| you were much more social or outgoing than usual; for example, you telephoned friends in the middle of the night?  | Yes/No |
| you were much more interested in sex than usual?   | Yes/No |
| you did things that were unusual for you or that other people might have thought were excessive, foolish, or risky?  | Yes/No |
| spending money got you or your family into trouble?  | Yes/No |
| 2. If you checked YES to more than 1 of the above, have several of these ever happened during the same period of time?   | Yes/No |
| 3. How much of a problem did any of these cause you—being unable to work; having family, money, or legal troubles; getting into arguments or fights? Please circle 1 response only |        |
| No problem Minor problem Moderate problem Serious problem  |        |
| Have any of your blood relatives (ie, children, siblings, parents, grandparents, aunts, uncles) had manic-depressive illness or bipolar disorder?                                  | Yes/No |
| For a positive screen, 7 of the 13 items in no. 1 must be yes, no. 2 must be yes, and no. 3 must be moderate or serious  |        |
| $^{a}$ A dapted with permission from Hirschfeld et al $^{22}$  |        |

## Table 5. The Composite International Diagnostic Interview (CIDI)<sup>a</sup>

I. Stem Questions

1. Some people have periods lasting several days or longer when they feel much more excited and full of energy than usual. Their minds go too fast. They talk a lot. They are very restless or unable to sit still, and they sometimes do things that are unusual for them, such as driving too fast or spending too much money. Have you ever had a period like this lasting several days or longer?<sup>b</sup>

2. Have you ever had a period lasting several days or longer when most of the time you were so irritable or grouchy that you started arguments, shouted at people, or hit people?

#### II. Criterion B Screening Questions

1. People who have episodes like this often have changes in their thinking and behavior at the same time, like being more talkative, needing very little sleep, being very restless, going on buying sprees, and behaving in ways they would normally think are inappropriate. Did you ever have any of these changes during your episodes of being excited and full of energy/very irritable or grouchy?

#### III. Criterion B Symptom Questions

Think of an episode when you had the largest number of changes like these at the same time. During that episode, which of the following changes did you experience?

- 1. Were you so irritable that you either started arguments, shouted at people, or hit people?<sup>c</sup>
- 2. Did you become so restless or fidgety that you paced up and down or couldn't stand still?
- 3. Did you do anything else that wasn't usual for you—like talking about things you would normally keep private or acting in ways that you would usually find embarrassing?
- 4. Did you try to do things that were impossible to do, like taking on large amounts of work?
- 5. Did you constantly keep changing your plans or activities?
- 6. Did you find it hard to keep your mind on what you were doing?
- 7. Did your thoughts seem to jump from one thing to another or race through your head so fast you couldn't keep track of them?
- 8. Did you sleep far less than usual and still not get tired or sleepy?
- 9. Did you spend so much more money than usual that it caused you to have financial trouble?

<sup>a</sup>Reprinted with permission from Kessler and Akiskal.<sup>23</sup>

<sup>b</sup>If this question is endorsed, the irritability stem question is skipped and the respondent goes directly to the criterion B screening question.

<sup>c</sup>This question is asked only if the euphoria stem question is endorsed.

Recently introduced, Web-based case-finding tools include the My Mood Monitor (M3), which consists of 27 questions to screen for bipolar disorder, MDD, anxiety, posttraumatic stress disorder (PTSD), and substance abuse.<sup>26</sup> Questions in the M3 are designed to assess both symptoms and functioning.<sup>27</sup>

Electronic health record-based case findings represent another emerging technique.<sup>28</sup> A screening tool for bipolar disorder that is incorporated into the electronic health record is activated automatically when a patient presents with depressive symptoms. Typically, the patient's responses are recorded by a health care assistant for later assessment by the physician.<sup>28</sup>

While case-finding tools are valuable supportive measures, it is important to stress that none are infallible. These tools can help the clinician to recognize patients who are likely to have the diagnosis and can improve the efficiency of the clinical interview by identifying symptoms that the clinician should pursue during the interview. However, they are not

| Subtype                                       | DSM-5 Definition   |
|---|--|
| Bipolar I disorder                            | ≥1 manic episode with/without psychotic features; the manic episode may have been preceded by hypomanic or major depressive episodes   |
| Bipolar II disorder                           | ≥1 major depressive episode accompanied by at least 1 hypomanic episode; no prior manic episode  |
| Cyclothymic disorder                          | Numerous periods of hypomanic and depressive symptoms for at least 2 years (adults);<br>do not meet criteria for a hypomanic or major depressive episode   |
| Other specified bipolar and related disorders | History of MDD and criteria for hypomania (except duration is <4 consecutive days)<br>History of MDD and hypomanic episodes with insufficient symptoms to meet criteria for<br>bipolar II disorder (although duration is ≥4 days)<br>Hypomanic episode without MDD<br>Short-duration cyclothymia |
| Specifiers for bipolar disorders              |  |
| Rapid cycling                                 | $\geq$ 4 episodes of manic, hypomanic, or major depressive episodes during a 12-month period   |
| Anxious distress                              | At least 2 of the following symptoms on most days during most recent mood episode:<br>Feeling keyed up or tense<br>Feeling unusually restless<br>Difficulty concentrating because of worry<br>Fear that something awful may happen<br>Feeling that individual might lose control                 |
| Mixed features                                | Manic or hypomanic episode, with mixed features  |
|   | Full criteria for a manic or hypomanic episode, with at least 3 of the following depressive symptom<br>Prominent dysphoria or depressed mood<br>Diminished interest or pleasure in activities<br>Psychomotor retardation<br>Fatigue or loss of energy  |
|   | Feelings of worthlessness or excessive or inappropriate guilt  |
|   | Recurrent thoughts of death  |
|   | Depressive episode, with mixed features  |
|   | Full criteria for a depressive episode, with at least 3 of the following manic/hypomanic symptoms:   |
|   | Elevated expansive mood  |
|   | Inflated self-esteem or grandiosity  |
|   | More talkative than usual or pressure to keep talking  |
|   | Flight of ideas or experience that thoughts are racing   |
|   | Increase in energy or goal-directed activity   |
|   | Increased or excessive involvement in activities that have high potential for painful consequence.<br>Decreased need for sleep   |

Abbreviation: MDD = major depressive disorder.

diagnostic instruments and cannot be used in place of the patient interview.<sup>14</sup>

## **The Patient Interview**

The detailed clinical interview formally establishes a diagnosis of bipolar disorder, based on a comprehensive history of past and current symptoms, augmented by medical records and family interviews (Figure 1). The clinical interview also can begin the process of educating the patient about the diagnosis and its impact.

In particular, the patient interview should establish<sup>2,14</sup>:

- The presence of past or current episodes of manic or depressive symptoms, as described for example in the *DSM-IV*, recently updated to *DSM-5* (Tables 2 and 3);
- The duration and severity of the episodes including the presence of suicidal or homicidal ideation;
- The impact of the episodes on functioning in work, social, and family roles;
- (4) The presence of comorbidities (such as substance abuse, personality disorder, and anxiety disorder including PTSD);

- (5) The history of treatments administered and the response to treatments;
- (6) The family history.

Besides establishing the diagnosis, these characteristics are an important element of treatment planning, helping to select the optimal medication(s) and the site of treatment whether in the primary care setting or involving specialist psychiatric support.

In cases of continued diagnostic uncertainty, the formal diagnosis of bipolar disorder may require a follow-up patient interview by an experienced primary care physician or psychiatrist to confirm the presence of *DSM-5* criteria, as well as to categorize the specific subtype of bipolar disorder that is present.<sup>5</sup>

Bipolar disorder is commonly divided into subtypes with distinct features, including I and II (Table 6). A classification of bipolar I disorder requires the presence of mania, while bipolar II disorder is distinguished by hypomania in combination with at least 1 major depressive episode.<sup>5</sup> Bipolar II disorder is more common than bipolar I, and the subtlety of the symptoms of hypomania may mean that bipolar II disorder is mistaken for MDD.<sup>29</sup> Clinical trials

## Table 7. Differential Diagnoses for Bipolar Disorder

Anxiety Disorders (including panic disorder, agoraphobia [fear of public places], social phobias, separation anxiety disorder, and generalized anxiety disorder)

Anxiety disorders commonly mimic, as well as co-occur with, bipolar disorder.<sup>33</sup> In particular, the physician may have to decide whether symptoms such as psychomotor acceleration, tension, or agitation are more appropriately explained by an anxiety disorder or hypomania (or both).<sup>31</sup> Cluster B personality disorders can also exhibit features, such as mood instability and impulsivity, that are common to mania or hypomania.<sup>31</sup> The chronic stress experienced by patients with anxiety disorders can induce depressive symptoms (for example, irritability, hopelessness, despair, emptiness, and chronic fatigue)<sup>30</sup>

Attention-Deficit/Hyperactivity Disorder (ADHD)

ADHD is characterized by overactivity, impulsive behavior, and poor judgment that can overlap with the symptoms of bipolar disorder. ADHD and bipolar disorder are also commonly present together. The co-occurrence of ADHD modifies the course of bipolar illness.<sup>34</sup> In the diagnosis of ADHD, the condition is formally recognized as a neurodevelopmental disorder

#### Major Depressive Disorder (MDD)

The symptoms of bipolar depression and MDD can be indistinguishable. Family history, treatment response, the frequency of recurrences, and (particularly) the presence of manic or hypomanic symptoms can all assist the physician to distinguish bipolar disorder from MDD<sup>14-16</sup>

#### Personality Disorders

Individuals diagnosed with personality disorders are particularly vulnerable to depression and substance use disorders.<sup>30</sup> Patients with substance abuse may have all 3 diagnoses. Personality disorders are classified in the *DSM*-5 as Axis II disorders; therefore, depression may frequently be diagnosed separately (from the personality disorder) as an adjustment disorder, dysthymia, or MDD<sup>30</sup>

#### Posttraumatic Stress Disorder

Characteristic *DSM-5* symptoms, categorized into 4 clusters (vs 3 clusters in the *DSM-IV*), include episodes in which the traumatic event or emotions linked to the event are reexperienced; nightmares, exaggerated startle responses; and withdrawal on a social, interpersonal, and psychological level. Anxiety and depression may feature as chronic symptoms. Posttraumatic stress disorder is classified as a trauma- and stressor-related disorder<sup>30</sup>

#### Schizoaffective Disorder and Schizophrenia

Chronic depression representative of MDD is observed in patients with schizoaffective disorder in addition to many of the symptoms of schizophrenia.<sup>30</sup> In those with schizophrenia, depression is frequently present because of their inherent difficulties in coping with the daily demands of living. The presence of depression adds an additional dimension to the treatment of patients with schizoaffective disorder and schizophrenia, specifically in helping the patients to gather themselves in the face of their depression to cope with their illness<sup>30</sup>

#### Substance Abuse

Substance abuse and dependence is one of the most common comorbidities in bipolar disorder, which may precede, exist with, or follow a mood episode.<sup>32</sup> The presence of substance abuse poses a particular diagnostic challenge to the physician, as it may itself be associated with a number of other disorders.<sup>31</sup> A comprehensive evaluation at the patient interview recognizing new *DSM-5* criteria such as a unified diagnosis of substance abuse and dependence (substance use disorder) and a severity specifier is key to establishing the diagnosis

have historically focused more on the treatment of bipolar I than bipolar II disorder.

**Confirmation of manic symptoms.** The DSM-5 criteria for mania or hypomania should be applied to all patients in whom a diagnosis of bipolar disorder is suspected or who provided a positive case-finding test (Table 2). DSM-5 criteria (compared with DSM-IV-TR) emphasize the importance of increased activity and energy in addition to mood in confirming the presence of manic or hypomanic symptoms. Physicians should also ensure that the manic symptoms identified are not better accounted for by other causes, such as substance abuse, concurrent medications, or other medical etiologies.

A review of the lifetime occurrence of manic episodes may reveal an exacerbation of symptoms over time, from initially mild episodes of hypomania, to mania accompanied by delusions, to delirious mania characterized by marked intensification of symptoms and a loss of self-control. In other patients, the intensity of symptoms never passes beyond hypomania.

**Confirmation of depressive symptoms.** Depression is the presenting symptom of bipolar disorder in most patients.<sup>10</sup> *DSM-5* criteria specify that depressed mood and/or a loss of interest or pleasure must be present for at least 2 weeks, in combination with the symptoms itemized in Table 3.<sup>5</sup> Physicians should ensure that the depressive symptoms identified are not better explained by other causes, including

medical conditions, alcohol or drug abuse, or bereavement.<sup>5</sup> Of particular importance for patients who are experiencing depressive symptoms is to assess for risk of suicide and self-harm. The *DSM-5* provides guidance on the prominence to be given to suicide prevention in treatment planning for an individual with bipolar disorder.

The *DSM*-5-based criteria for diagnosing a bipolar depressive episode are identical to those for MDD,<sup>5</sup> and additional clinical features including past and concurrent symptoms are required for differential diagnosis (Figure 2). The depressive symptoms of bipolar disorder can also be attributed mistakenly to a number of other disorders, notably PTSD, anxiety disorders, schizoaffective disorder and schizophrenia, and personality disorders (Table 7).<sup>14–16,30–34</sup>

**Confirmation of mixed features.** The presence of depressive features during a manic episode or manic features during a depressive episode confirms the presence of mixed features.<sup>5</sup> Insomnia, agitation, appetite changes, psychotic features, and suicidal ideation are common presenting symptoms.<sup>5</sup> It is important to eliminate other potential causes of a mixed state, among which are antidepressant medications, electroconvulsive or light therapy, and medical treatments (eg, corticosteroids).

Patients who experience mixed episodes or features may, over time, progress to depressive-only episodes or, less frequently, to manic-only episodes.<sup>5</sup>

*Functioning.* Certain behaviors that are commonly associated with bipolar disorder can help to establish the diagnosis.<sup>35</sup> These behaviors may include instabilities related to the patient's family (eg, estrangement from the family of origin, divorce, frequent remarriage) or employment (frequent job changes, difficulties at work, unemployment), financial difficulties (bankruptcy, "boom and bust" cycles), or a history of impulsive or reckless behavior (sexually transmitted infections, unwanted pregnancies, substance abuse, accidents).

Understanding the severity and the type of functioning disorder can help to differentiate mania from hypomania. Disinhibition, poor judgment, risk-taking, and aggressive behaviors are all associated with a more severe, manic episode.<sup>5,35</sup>

**Comorbidities.** Patients with bipolar disorder are predisposed to other psychiatric disorders at elevated rates. Anxiety disorders (such as PTSD), personality disorder, ADHD, and alcohol or drug dependence are particularly common comorbidities.<sup>36,37</sup> The *DSM-5* acknowledges the clinical evidence that anxiety is an important modifier of bipolar prognosis by incorporating the disease specifier "anxious distress" in the diagnosis of bipolar disorder (Table 6).

Certain chronic physical conditions are also commonly found in the bipolar population, such as cardiovascular and metabolic disorders. Obesity, for example, affects about onehalf of patients with bipolar disorder.<sup>38</sup> These conditions may in part reflect the lifestyle and behaviors associated with bipolar disorder, and they can significantly shorten life expectancy.<sup>39,40</sup>

## **Family History**

Family history can be highly informative for diagnosing bipolar disorder. Between 80% and 90% of bipolar patients describe family members with a history of mood disorders including bipolar disorder and MDD.<sup>41</sup> The children of bipolar patients are also at elevated risk (most studies suggest a 5%–15% risk<sup>42,43</sup>) of developing bipolar disorder,<sup>44</sup> indicating a strong genetic element in the predisposition to the condition. Of note, the "absent" parent or other relative—for instance, one who might have abandoned the family, been incarcerated, or was deceased when the current patient was a child—may, on further inquiry, be likely to have had a bipolar condition.

## **Other Elements of the Patient Interview**

*Physical examination.* Physical examination cannot confirm a diagnosis of bipolar disorder, but it can, in combination with the medical history, help exclude the diagnosis by identifying illnesses that mimic bipolar symptoms.<sup>2,33</sup> For example, a physical examination may identify hypothyroidism or hyperthyroidism, which are associated respectively with depressive and manic symptoms.

*Laboratory tests and imaging.* No laboratory test is required to establish the diagnosis of bipolar disorder.

However, in conjunction with the physical examination, laboratory tests can help to exclude alternative etiologies for mood symptoms.<sup>2</sup> Laboratory tests may include a urine toxicology screen (in cases in which substance misuse is suspected but denied) and a complete blood count (to exclude infection or anemia as potential causes of depression). Fasting glucose and lipid assessments are important for establishing the presence of diabetes or hyperlipidemia and for determining baseline values before initiation of treatment. MRI or other neuroimaging techniques are rarely indicated, but in selected cases can be valuable to exclude an organic etiology for mood symptoms, such as a brain tumor or multiple sclerosis in cases of recent-onset mania.<sup>45</sup>

*Treatment response.* A history of a lack of response to antidepressant monotherapies may suggest that a patient has bipolar disorder rather than MDD. Any patient who has experienced no symptom benefit from multiple trials of antidepressants should be reassessed for bipolar disorder. Conversely, patients who demonstrate a significant treatment response to antidepressant monotherapy or in whom the response is very rapid should be screened for possible precipitation of a manic/hypomanic episode.<sup>46,47</sup>

**Differential diagnosis.** A number of common psychiatric disorders may mimic the symptoms of bipolar disorder and should be considered in the differential diagnosis.<sup>31</sup> These disorders are summarized in Table 7.

## The Family/Partner Interview

A history of the patient's symptoms obtained from a relative or close friend (with the patient's consent) can be highly informative, given that bipolar patients frequently lack insight into their own behavior and the effects of their behavior on others.<sup>48</sup> In other cases, the family will not be aware of the bipolar patient's condition.

Once a bipolar diagnosis is established, the primary care physician can offer considerable practical support to both the patient and family, helping them to cope with daily life activities and to prepare for stressful life transitions such as moving away to college, entering the job market, marrying, and starting a family.

## MANAGING THE BIPOLAR PATIENT IN PRIMARY CARE

Decision steps in bipolar management are summarized in Table 8.

## **Establishing a Care Pathway**

Patients in danger of self-harm or of causing harm to others require immediate specialist psychiatric intervention, which may entail escorted transport from the primary care setting. The preparation of a management plan that specifies the current medications and other information relevant to the emergency services will assist the transition from primary to specialist care.

For other patients, primary care physicians should decide on the level of intervention that they wish to offer: whether providing acute and longer-term treatment themselves or

#### Table 8. Clinical Decision Steps in Bipolar Management

- 1. Determine whether there is a need for immediate specialist psychiatric intervention
- Consider the resources and the multidisciplinary team required for successful management in primary care
- 3. Set treatment goals and select evidence-based treatment(s) for acute and long-term treatment, involving the patient in decision-making whenever possible
- 4. Gain familiarity with the monitoring recommendations for continued patient care, including ongoing evaluations of bipolar symptoms and functioning, treatment-related adverse effects, adherence, and general health status

involving specialist psychiatric intervention (through referral or as collaborative care) (Figure 1). The ability of a primary care physician to offer successful care to a bipolar patient depends on factors such as the severity of the condition, its complexity (including the presence of comorbidities), the wishes of the patient, the experience of the physician, and the organization of the practice team. It is the rare primary care physician who has the expertise, time, and resources available to manage bipolar I patients, particularly during their manic phases.

Organization of a practice team entails effective staff training and coordination, provision of patient-monitoring systems, and establishment of links to referral and support services.49,50 A patient-centered, collaborative team approach that includes health care professionals with complementary skills offers the greatest likelihood of success.<sup>49-52</sup> This team typically includes nursing staff, community support workers, and specialist psychiatrics and psychologists, with the primary care physician taking a coordinating role at the center.<sup>1,52</sup> The primary care physician and psychiatrist should communicate frequently regarding any change in patient symptoms or functioning and should have an explicit understanding between them and with the patient regarding the management of medications. Because of the potential for drug-drug interactions with medications used for common comorbid medical conditions, both the psychiatrist and primary care physician should keep the other informed of any medication adjustments at the times they are being made.

# Treatment Principles: Pharmacologic and Nonpharmacologic Treatments

For most patients, the foundation of acute and maintenance treatment is pharmacologic therapy.<sup>53,54</sup>

Acute pharmacologic treatment has the objective to reduce symptoms promptly with acceptable safety and tolerability. The treatment that is selected is based on the characteristics of the mood episode (ie, its polarity and symptom severity) and on the patient's general health status, including the presence of concurrent medical conditions such as diabetes or obesity, which can be exacerbated by certain therapies. A lack of response or an adverse effect to a medication may prompt a change in dose or a switch to another medication class. For many patients, particularly those with severe manic episodes or mixed states, combination therapy may be required—either using 2 or more medications concurrently or by the introduction of psychosocial approaches.<sup>55–57</sup>

Approximately 1 in 5 bipolar patients will eventually require 4 or more concomitant pharmacologic medications to control their symptoms.<sup>58</sup> High rates of comedication use are particularly common in patients with a high burden of depressive symptoms and at elevated risk for suicidality.<sup>58</sup> While combination therapy may provide greater symptom control, it is also associated with an increased burden of adverse effects, cost, and potential for drug-drug interactions.<sup>59</sup>

## **Acute Treatments**

*Manic symptoms.* Established medications for the treatment of manic symptoms include lithium, divalproex, carbamazepine, and the atypical antipsychotics asenapine, aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone (Table 9).<sup>51,60,61</sup>

Lithium is a conventional mood stabilizer with a slower onset of action than the antipsychotics. The need to dose titrate lithium to reduce its toxicity also delays the time to achieve a response.<sup>62</sup> Lithium is associated with a moderate improvement in symptoms in 40%–80% of patients after 2 to 3 weeks of treatment for acute mania.<sup>63</sup> Lithium is one of the few medications that has been demonstrated to reduce the occurrence of suicide.<sup>64</sup> Divalproex and carbamazepine are at least as effective in reducing symptoms as lithium, with a faster onset of action.<sup>63</sup> More than one-half of patients treated with divalproex or carbamazepine experience significant improvement in their manic symptoms.<sup>63</sup>

Atypical antipsychotics have gained widespread acceptance as a first-line treatment in mania,<sup>55</sup> offering the advantage over typical antipsychotics of a reduced propensity to extrapyramidal adverse effects.<sup>65</sup> Each of the atypical antipsychotics has broadly similar efficacy in the treatment of acute mania, with response rates ranging from 49%–73% across different studies.<sup>63</sup> Trial evidence does point, however, to characteristic differences in the safety profile of these agents (discussed below).

Combination therapy for patients whose manic symptoms fail to respond to monotherapy frequently consists of a mood stabilizer (eg, lithium, divalproex, or carbamazepine) with an atypical antipsychotic.<sup>45,66</sup>

**Depressive symptoms.** When compared with mania, there are few medications with proven efficacy in the treatment of acute bipolar depression, particularly bipolar II depression. Quetiapine monotherapy, olanzapine in combination with fluoxetine, and (most recently) lurasidone monotherapy or in combination with lithium or valproate are the sole US Food and Drug Administration (FDA)–approved medications for bipolar I depression, while only quetiapine is approved for bipolar II depression.<sup>55</sup> Lamotrigine showed a small but significant improvement in depressive symptoms compared with placebo in a pooled analysis of 5 acute randomized controlled trials,<sup>67</sup> but 4 of these 5 studies were underpowered and failed to show a superiority of lamotrigine over placebo.<sup>68</sup>

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| Table 9. US Food and Drug Administration–Approved Oral Medications in the Treatment of Adults With Bipolar Disorder <sup>a</sup> |  |  |   |  |
|--|--|--|---|--|
| Medication   | Mania  | Depression   | Mixed   | Maintenance  |
| Lithium  | $\checkmark$   | _  | _   | $\checkmark$   |
| Carbamazepine, carbamazepine extended release  | $\checkmark$   | —  | $\checkmark$  | —  |
| Lamotrigine  | _  | _  | _   | $\checkmark$   |
| Divalproex, divalproex extended release  | $\checkmark$   | _  | _   | _  |
| Aripiprazole   | <ul> <li>✓ (monotherapy and<br/>adjunctive therapy)</li> </ul> | _  | <ul> <li>✓ (monotherapy and<br/>adjunctive therapy)</li> </ul>                            | <ul> <li>✓ (monotherapy and<br/>adjunctive therapy)</li> </ul>   |
| Asenapine  | <ul> <li>✓ (monotherapy and<br/>adjunctive therapy)</li> </ul> | _  | <ul> <li>✓ (monotherapy and<br/>adjunctive therapy)</li> </ul>                            | _  |
| Lurasidone   | _  | <ul> <li>✓ (monotherapy and<br/>adjunctive therapy)</li> </ul> | —   | _  |
| Olanzapine   | √ (monotherapy and<br>adjunctive therapy)                      | ✓ (combined with fluoxetine)                                   | <ul> <li>✓ (monotherapy and<br/>adjunctive therapy)</li> </ul>                            | √ (monotherapy)  |
| Quetiapine immediate release,<br>extended release  | ✓ (monotherapy and<br>adjunctive therapy)                      | √ (monotherapy)  | <ul> <li>✓ (extended release only:<br/>monotherapy and<br/>adjunctive therapy)</li> </ul> | $\checkmark$ (adjunctive therapy)  |
| Risperidone  | <ul> <li>✓ (monotherapy and<br/>adjunctive therapy)</li> </ul> | _  | √(monotherapy and adjunctive therapy)   | <ul> <li>✓ (risperidone long-acting<br/>injection only: monotherapy<br/>and adjunctive therapy)</li> </ul> |
| Ziprasidone  | ✓ monotherapy)   | _  | √ (monotherapy)   | ✓ (adjunctive therapy)   |

symbols: √ = approved, -= not approved

The role of lamotrigine in the maintenance treatment and prevention of depressive episodes is more convincing, with 2 favorable, randomized, placebo-controlled trials that have led to FDA approval of lamotrigine for this indication.<sup>69,70</sup>

Quetiapine is the only medication that is FDA approved as monotherapy for the treatment of both manic and depressive episodes of bipolar disorder.<sup>71</sup> The extended-release (XR) formulation of quetiapine is approved for once-daily dosing for both manic and depressed episodes, while the immediate-release (IR) formulation of quetiapine is dosed twice daily for bipolar mania and once daily for bipolar depression.<sup>72,73</sup> A medication with broad-spectrum moodstabilizing potential may offer opportunities for simplified therapy in specific patients.<sup>74</sup> It may also be noted that the XR formulation of quetiapine, aripiprazole, and lurasidone are the only atypical antipsychotics approved as adjunctive therapy in MDD.<sup>73,75</sup> Compared with the IR formulation, quetiapine XR offers the benefit of once-daily dosing in all approved indications, which is achieved through its distinct pharmacokinetic profile, characterized by a lower peak concentration and more stable plasma concentrations over time.<sup>76</sup> Quetiapine XR also has a distinct tolerability profile relative to the IR formulation, including a reduction in sedation intensity during initial dose escalation.<sup>76–78</sup>

Mixed features/mixed episodes. Divalproex and the atypical antipsychotics (aripiprazole, olanzapine, quetiapine XR, risperidone, ziprasidone, and asenapine) are recommended as first-line treatments for mixed states.<sup>79</sup> By contrast, lithium does not appear to confer significant benefit in mixed states.<sup>2</sup> Combination therapies, typically including an atypical antipsychotic and a mood stabilizer, are likely to be required for many patients experiencing mixed states.79

#### **Maintenance Treatments**

Maintenance treatment can reduce, although not entirely eliminate, the recurrence of mood episodes. In part, this limitation reflects the limited efficacy of medications, but, in part, it is also explained by poor adherence, which is encouraged by a suboptimal symptom response or the development of treatment-related adverse effects.<sup>80,81</sup>

In many patients, the medications that were effective for the acute phase are the first choice in maintenance treatment.55 Lithium at optimal doses reduces the rate of recurrence by 50% in clinical trials.<sup>63</sup> The long-term benefits of lithium are hindered by poor adherence due to the narrow therapeutic window and significant adverse effects.<sup>82</sup> Lithium is generally associated with greater efficacy in the prevention of manic rather than depressive episode recurrences,<sup>45,63</sup> which is consistent with its predominantly antimanic effects in acute treatment. Divalproex has an efficacy equivalent to lithium for the prevention of recurrence,<sup>83</sup> while carbamazepine may be found to be more effective than lithium in patients with atypical features, such as mixed states and delusion.63

Among the atypical antipsychotics, olanzapine, risperidone (long-acting injection), and aripiprazole are approved as monotherapies for maintenance treatment, while quetiapine and ziprasidone are approved in combination with lithium or divalproex for prevention of recurrence.<sup>60,71,84,85</sup> Combining a mood stabilizer and an antipsychotic agent generally provides superior relapse prevention compared to single agents alone.86,87

## Adverse Effects of Pharmacologic Treatments

All primary care physicians, whether or not they participate in the management of bipolar symptoms, should

| Treatments for Bipolar Disorder <sup>a</sup> |  | Treatments <sup>a</sup>                                 |   |  |
|--|--|---|---|--|
| Treatment                                    | Notable Adverse Effects  | Treatment   | Recommended Monitoring  |  |
| Lithium                                      | Thirst, polyuria, diabetes insipidus<br>Sedation<br>Tremor<br>Weight gain<br>Diarrhea, nausea<br>Cognitive effects   | Lithium   | Serum drug levels every 3 to 6 mo once stable<br>levels have been reached<br>Electrolytes, urea, creatinine every 3 to 6 mo<br>(to exclude renal impairment)<br>Thyroid-stimulating hormone, calcium, and<br>weight after 6 mo and annually thereafter          |  |
| Carbamazepine                                | Headache<br>Fatigue  | Calandar  | (to exclude thyroid or parathyroid<br>abnormalities)  |  |
|  | Nystagmus<br>Ataxia<br>Rash (including Stevens-Johnson syndrome and<br>toxic epidermal necrolysis)<br>Leukopenia, hyponatremia                             | Carbamazepine   | Serum drug levels during treatment initiation<br>and then as clinically indicated<br>Conduct complete blood count, liver function<br>tests, and electrolytes, urea, and creatinine<br>assessments monthly for 3 mo and annually                                 |  |
| Divalproex, divalproex<br>extended release   | Tremor<br>Sedation<br>Weight gain<br>Nausea  |   | to exclude blood dyscrasias, liver failure,<br>hyponatremia<br>Monitor for rash (to exclude Stevens-Johnson<br>syndrome)  |  |
|  | Diarrhea<br>Hair loss<br>Leukopenia, thrombocytopenia<br>Elevated liver transaminase levels, hepatic<br>failure, pancreatitis<br>Polycystic ovary syndrome | Divalproex  | Serum drug levels during treatment initiation<br>and then as clinically indicated<br>Conduct weight, complete blood count,<br>menstrual history, and liver function tests<br>every 3 mo (first year) and annually to<br>exclude thrombocytopenia, dysmenorrhea, |  |
| Lamotrigine                                  | Dizziness, tremor<br>Somnolence, headache<br>Dry mouth, nausea   | Lamotrigine   | Monitor for rash (to exclude Stevens-Johnson<br>syndrome)   |  |
|  | Rash (including Stevens-Johnson syndrome and<br>toxic epidermal necrolysis)<br>Leukopenia, thrombocytopenia, pancytopenia<br>Aseptic meningitis            | Atypical antipsychotics                                 | Assess weight monthly for 3 mo and every<br>3 mo thereafter<br>Blood pressure, blood glucose and serum<br>linids every 3 mo and annually thereafter to  |  |
| Atypical antipsychotics                      |  |   | exclude metabolic syndrome  |  |
| Aripiprazole                                 | Akathisia, other EPS, sedation, hyperglycemia  |   | Monitor for abnormal movements (to exclude  |  |
| Asenapine                                    | EPS, sedation, dyslipidemia, hyperglycemia   |   | extrapyramidal symptoms)  |  |
| Lurasidone                                   | Akathisia, other EPS, somnolence, nausea, vomiting, diarrhea, and anxiety  |   | Conduct electrocardiogram or prolactin<br>evaluation as clinically indicated  |  |
| Olanzapine                                   | Sedation, weight gain, EPS (less frequent),  | <sup>a</sup> Based on Connolly and Thase. <sup>55</sup> |   |  |
| Quetiapine                                   | Sedation, weight gain, EPS (less frequent),<br>dyslipidemia, hyperglycemia   |   |   |  |
| Risperidone                                  | EPS, sedation, hyperprolactinemia,<br>dyslipidemia, hyperglycemia  | Children and a  | dolescents with bipolar disorder may  |  |
| Ziprasidone                                  | EPS, sedation, agitation, dyslipidemia,  |   |   |  |

# Table 10. Characteristic Adverse Effects of Pharmacologic

Table 11. Recommended Monitoring for Pharmacologic

Abbreviation: EPS = extrapyramidal symptoms. be aware of the safety profiles of the medications used in

bipolar disorder (Table 10).55,56 The potential of lithium to cause progressive renal

hyperglycemia

<sup>a</sup>Based on Price and Marzani-Nissen<sup>2</sup> and Chung et al.<sup>51</sup>

insufficiency and fatalities through overdose should be considered when making long-term therapy choices,<sup>88</sup> as should the deleterious effects of lithium, divalproex, and carbamazepine during pregnancy.55,88 A main concern with lamotrigine is the serious, although rare, side effect of Stevens-Johnson-like rash.55

The adverse effects of atypical antipsychotics differ between the individual agents.<sup>55,89-92</sup> Olanzapine is associated with a higher risk of weight gain, diabetes mellitus, and dyslipidemia than other antipsychotics.<sup>89-91</sup> Risperidone induces marked hyperprolactinemia, whereas other atypical antipsychotics have minimal or even favorable effects on prolactin.93 Ziprasidone is reported to have a lower risk for weight gain, and quetiapine has a decreased risk for extrapyramidal symptoms relative to risperidone.94

with olanzapine, as well as the extrapyramidal symptoms and metabolic changes reported with other atypical antipsychotics.95 Monitoring Long-term monitoring for medication adverse effects is essential to ensure continued safety (Table 11).<sup>2,55,62</sup> As

mentioned previously, the propensity to weight gain and dyslipidemia is particularly high for olanzapine, although other atypical antipsychotics carry some level of risk.90,95 The presence of cardiometabolic factors may signal the impending development of metabolic syndrome (which also includes hyperglycemia and hypertension), a condition that is a precursor to diabetes and cardiovascular disease. Prevention of these metabolic disorders and related premature death warrants dedicated routine monitoring for weight gain, blood pressure, and increases in triglyceride and glucose levels.2,96

Physicians must also monitor patients closely for emergence of mania or psychosis, changes in functioning and disability, and subjective reports of depressive symptoms and quality of life.<sup>97</sup> A rapid reinitiation or modification to

| Table 12. | . Early Signs of Relapse (in order of | decreasing |
|-----------|---------------------------------------|------------|
| frequence | cy) <sup>a</sup>                      |            |

| inequency/   |                       |  |  |
|--|-----------------------|--|--|
| Mania  | Depression            |  |  |
| Sleep disturbance                                  | Low mood              |  |  |
| Psychotic symptoms                                 | Psychomotor symptoms  |  |  |
| Mood change  | Increased anxiety     |  |  |
| Psychomotor symptoms                               | Appetite change       |  |  |
| Appetite changes                                   | Suicidal ideas/intent |  |  |
| Increased anxiety                                  | Sleep disturbance     |  |  |
| <sup>a</sup> Based on Jackson et al. <sup>98</sup> |                       |  |  |

therapy may be required if prodromal symptoms (eg, sleep disruption, increased irritability, resumption of substance use) or full-blown episodes emerge (ie, it is important to "treat the disease, don't blame the patient"). Given the high frequency of coexisting medical conditions in bipolar disorder, routine monitoring should include an evaluation for medical morbidities.<sup>2,55,59</sup>

Patient and family education has been shown to enhance the success of goal-setting, decision-making, and collaboration with the health care team, thereby increasing the likelihood of an improved long-term outcome.<sup>52</sup> In particular, educating patients on how to monitor their symptoms for signs of impending relapse can assist physicians in monitoring and management (Table 12).<sup>50,98</sup> Patient-directed educational resources are widely available to support health care professionals in this regard.<sup>99,100</sup>

## Adherence

The primary care physician has a fundamental role in encouraging adherence. Nonadherence to medication is an acknowledged barrier to effective treatment over the long term.<sup>101</sup> Discussion of the treatment options available and their possible adverse effects (and how to manage them) can enhance treatment adherence. Patients may give many reasons for nonadherence to medication, but a common underlying reason is a lack of insight into the impact of symptom recurrence.<sup>101,102</sup> Encouraging patient education and forging a therapeutic alliance between physician and patient helps to maintain adherence to therapy.<sup>103,104</sup>

## **Psychosocial Treatments**

While outside the remit of this review, psychosocial treatments—psychoeducation, cognitive-behavioral therapy, family-focused therapy, and interpersonal and social rhythm therapy—have an established role in management, with efficacy in regularizing daily activities, reducing substance misuse, identifying early warning signs of relapse, and enhancing medication adherence.<sup>105</sup>

## **General Medical Care**

Patients with bipolar disorder have an increased incidence of certain medical comorbidities and are at elevated risk of early death, particularly cardiovascular-related death.<sup>40</sup> Medications used in the treatment of bipolar disorder can cause weight gain, lipid abnormalities, and other long-term effects, which may exacerbate the propensity to medical complications.<sup>106</sup> Bipolar patients are also at elevated risk of not following routine preventive health care measures. For this reason, preventive care tactics tailored to the individual patient, such as hepatitis immunization or long-term birth control methods, are the most appropriate. Because sleep changes may trigger (as well as be an indicator of) a change in mood states, interventions to improve sleep can be helpful in this population.

For women who are pregnant, it is essential that treatment is maintained to stabilize their mood. The choice of the treatment administered requires careful consideration, given the potential teratogenicity of medications including lithium, divalproex, and carbamazepine.<sup>55</sup>

## CONCLUSION

Primary care physicians are the initial as well as the continued point of contact for many patients with bipolar disorder, with responsibility for accurate diagnosis and appropriate ongoing care. Diagnostic accuracy can be improved by attentiveness to the key symptoms and signs of bipolar disorder. Pharmacologic and psychosocial treatments can provide effective management for manic and depressive symptoms and maintain remission over the long term in many patients.

As with any chronic illness, the objective of working with bipolar patients to improve their adaptive and problemsolving skills and their self-management and self-monitoring skills should be a priority. Ensuring that both patient and family are familiar with local and national support networks will also be helpful.

Whether they manage bipolar patients directly or refer them to specialist psychiatric care, primary care physicians are vital to the long-term management of these patients, both through re-engaging them with therapy for future mood episodes and in ensuring that they obtain quality preventive and chronic disease care.

*Drug names:* aripiprazole (Abilify), asenapine (Saphris), carbamazepine (Carbatrol, Equetro, and others), divalproex (Depakote and others), fluoxetine (Prozac and others), lamotrigine (Lamictal and others), lithium (Lithobid and others), lurasidone (Latuda), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others), ziprasidone (Geodon).

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**Potential conflicts of interest: Dr Culpepper** has served as a consultant for Forest, H. Lundbeck A/S, Merck, Sunovion, and Takeda and has made presentations regarding a federally funded study of methods to reduce hospital readmissions (with no mention of pharmaceutical agents) supported through Merck's speaker's bureau. **Funding/support:** Writing of the manuscript was funded by AstraZeneca.

*Acknowledgment:* The author thanks Bill Wolvey, BSc, of PAREXEL for medical writing support, which was funded by AstraZeneca. *Disclaimer:* Dr Culpepper, the journal's editor in chief, was not involved in the editorial review or decision to publish this article.

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