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# MANAGEMENT OF BIPOLAR PSYCHOSIS:

## Diagnosis and Treatment Strategies



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## LEARNING OBJECTIVES

1. You will be able to accurately diagnose bipolar disorder within the clinical setting, based on criteria delineated in current expert guidelines.
2. Using the guideline recommendations, you will be able to select effective pharmacologic agents to interrupt the psychosis and to create a long-term treatment plan that maintains stability in patients and minimizes chances of recurrence, suicide, and medication adverse effects.
3. You will be able to integrate evidence-based nonpharmacologic approaches into a comprehensive treatment plan.
4. You will be able to identify and manage comorbidities (including substance use disorder and attention-deficit/hyperactivity disorder) and women's disorders (eg, postpartum psychosis, premenstrual syndrome, polycystic ovary syndrome).

## INTRODUCTION

In any given year, bipolar disorder affects 5.7 million US adults (approximately 2% of the US population 18 or older), and only 69% of these people may be accurately diagnosed and treated for the condition.<sup>1</sup> Worldwide figures are comparable. According to the World Health Organization, the median rate of untreated bipolar disorder is 50.2%.<sup>2</sup> Between symptom onset and correct diagnosis, patients may consult as many as 4 physicians, and 8 to 10 or even 20 years may elapse.<sup>1,3,4</sup>

Bipolar disorder is most commonly misdiagnosed as unipolar depression because patients often present while at the depressive rather than the manic "pole"<sup>5,6</sup>—or they present with depression in addition to psychosis.<sup>7</sup> Patients misdiagnosed with unipolar depression often receive costly and inappropriate treatment—overuse of antidepressants and underuse of potentially effective medications.<sup>8</sup> Misuse of antidepressants is a particular problem because these medications can trigger or exacerbate mania in patients with bipolar disorder.<sup>9</sup>

Another misdiagnosis for bipolar psychosis is schizoaffective disorder.<sup>10</sup> Differentiating these conditions can be difficult. Although initial treatments for psychosis and schizoaffective disorder may be similar, misdiagnosis has long-term implications for appropriate maintenance (as discussed later in this monograph).

Various factors can impede correct diagnosis of bipolar disorder. Medical and neurologic disorders with symptoms of psychosis are too often ignored during the diagnostic workup. Nonwhite patients who present with psychosis are less likely than white patients to receive a diagnosis of primary mood disorder, and more likely to receive a diagnosis of psychotic disorder; Black patients who present with psychosis are more likely to be diagnosed with schizophrenia, and Hispanic patients are more likely to be diagnosed with major depression.<sup>11-14</sup> Patients in lower socioeconomic classes may be especially at risk for misdiagnosis. Older adults presenting with late-onset bipolar disorder are sometimes misdiagnosed with an organic brain disorder.<sup>15</sup> Adults older than 50 more often present with depressive versus manic symptoms;<sup>16</sup> thus, they may receive a misdiagnosis of depressive psychosis, a less common disorder. However, late-onset symptoms must be carefully evaluated for medical and neurologic causes.

Patients with undiagnosed bipolar disorder are at increased risk for suicide.<sup>17</sup> Moreover, each psychotic episode may place the patient at risk for longer episodes and decreased time between episodes.

Misdiagnosis may ultimately lead to increased functional impairment and decreased quality of life, as well as increased financial burden for patient, family, and society.<sup>18</sup>

This monograph is designed to help psychiatrists correctly diagnose bipolar disorder that presents with psychosis, and to individualize treatment that incorporates pharmacologic and nonpharmacologic interventions. Also discussed are ways to address common challenges, which include preventing recurrence and suicide, engaging patient and family, addressing women's needs, identifying and treating comorbidities, and managing adverse effects of medications. Familiarity with and adherence to evidence-based treatment guidelines are emphasized, as they have been shown to improve overall patient outcomes.<sup>19</sup> Although the monograph will touch on depressive psychosis and mixed states, its primary focus will be on manic psychosis.

## TWO CASES

Like fever, psychosis is a symptom of several disorders that often present similarly. Correctly diagnosing a patient who presents in a psychotic state can be challenging. Consider the following cases.

### Ms B

Ms B, a 26-year-old black woman, is brought to the emergency department by her roommates. She appears agitated and speaks rapidly and loudly about “creating safe and sexually open homes for humanity.” She is wearing only a bra and panties under a dirty raincoat, which she reports receiving as a gift from a homeless man. She announces that she is a social worker and should be “running the hospital” instead of “sitting in the ER like a lowly patient.” When she attempts to push aside the triage nurse and occupy her chair, she is restrained and sedated.

*History of present illness.* Ms B's parents are contacted, and a history is obtained. Ms B has always been high-functioning, and there is no previous history of psychosis. However, there is a previous history of “mood swings.” When she had a depressive episode in high school, her parents took her to a psychiatrist, who prescribed the antidepressant fluoxetine. Ms B “sped up” and felt as though she were “spinning.” She told her parents that these sensations were “a lot of fun,” but she stopped using the antidepressant because of weight gain and libido suppression.

Ms B's roommates report that living with her is like “living with a roller coaster” because her moods fluctuate so dramatically. During recent months, she has been speaking rapidly, calling acquaintances and friends late at night, and entering other people's rooms without permission. During the past weeks, she has been obsessing about her sexuality, prominently displaying her cleavage, and boasting about her sexual prowess. Last night, she slept with a homeless man. This morning, her roommates asked her to move out. She became agitated but eventually agreed to accompany them to the hospital after they told her she might meet homeless people in the emergency room.

Ms B is a social work student in a field placement at a homeless shelter. She stopped attending classes and has not met with her advisor for several weeks. She has become obsessed with wanting to “cure” homeless people by “liberating their sexuality” and has contacted several local government officials with an elaborate plan to resettle the homeless in “sexually open environments.”

*Medical history.* For a brief time during her first year of high school, Ms B was bulimic. She stopped bingeing and purging after watching a

television program about a bulimic girl with a ruptured esophagus. Ms B does not smoke, drink alcohol, or use recreational drugs.

*Medication history.* Ms B takes no medications.

*Family history.* Ms B's father has type 2 diabetes and hypertension. There is a family history of depression on her mother's side, and Ms B's first cousin committed suicide.

*Physical examination.* Ms B is obese, with a body mass index of 30.6. She has hair growth on the upper lip, chin, and chest. On questioning, she says she has amenorrhea. Given Ms B's excessive weight and family history of diabetes, the clinician orders fasting blood glucose and other routine laboratory tests. All test results are normal, except for elevated blood sugar (110 mg/dL).

### Mr E

Mr E, a 29-year-old white, non-Hispanic man, is taken by his parents to the emergency department. The parents, each holding one of his arms, drag him to the triage desk. Crying, Mr E begs them to take him home: he believes the hospital staff are government agents who want to kill him because they know he is working on a spaceship that will “transport people into space so they can survive the nuclear war the government is orchestrating.” He engages in a series of repetitive hand motions “to ward off the invasion of his mind and signal to the Martians to keep him safe.” When the triage nurse asks him a question, he accuses her of “tricking him into submitting to the government” and lunges at her; he is then restrained and sedated.

*History of present illness.* Mr E's parents report that he has always been “different.” For example, when he was a child, he talked to himself and played with toy spaceships long after such play was no longer age-appropriate. He has always muttered incongruously in private as well as social contexts, moving his hands about in “bizarre” patterns. He always had “strange ideas,” stating that the government was “out to get him” and that “only in space would he be safe.” Sometimes he claimed to see “Martians standing at his bedside to protect him.” Ever since childhood, he has been ridiculed for his odd behaviors. His mother reports that he experiences fluctuating moods. “Usually he's okay—I mean, he's never ‘normal,’ but at least he's not up or down. But at other times he's really sad.” She admits that his “down” times are easier to live with than the “up” times because “when he's down, he just lies around and doesn't bother anyone, though he cries a lot, but when he's up, he's edgy, a little hyper and especially silly—a real pain.”

After completing high school, Mr E began taking courses at a community college, only to drop out and take a job as a waiter. His employment since then has been intermittent, and the jobs he has taken (mostly odd jobs) have been short-lived because of his “peculiar behavior.” He has refused counseling and medication, stating his belief that his secrets will not be safe and that he will be poisoned.

A week before presenting to the emergency department, Mr E watched a news program about people who believe that the September 11, 2001 attacks on the United States were the outcome of a conspiracy planned by the US government. He became agitated and began refusing to eat food that did not come in a cellophane package. He took to his bed, and his mother heard him “praying to the Martians.” After he threw his breakfast (“poisoned by the government”) across the room, his parents took him to the hospital.

*Medical history.* Mr E has no history of medical problems beyond the usual childhood illnesses. He is a heavy smoker (2 packs a day) but

does not use alcohol or recreational drugs.

**Medication history.** Mr E takes no medications.

**Family history.** Mr E's father has ulcers and esophagitis, and his mother has "nervous tension" and insomnia, which she medicates with alprazolam and zolpidem, respectively. There is a strong history of "eccentricity" on the father's side of the family. Mr E's grandfather was reportedly "totally bonkers" (no formal diagnosis was made), and his uncle is schizophrenic.

**Physical examination.** Mr E's physical examination and laboratory evaluations are unremarkable.

### Commentary

Ms B and Mr E have both presented with symptoms of severe psychosis—delusions, inappropriate behavior, bizarre and disorganized thinking, agitation, and aggression. Both patients have a history of fluctuating moods. The differential diagnosis is bipolar disorder or schizoaffective disorder. How can the clinician distinguish these conditions? Furthermore, could the psychosis in either or both cases have a different origin?

## DIAGNOSING BIPOLAR DISORDER IN PATIENTS WITH PSYCHOSIS

The first task is to identify and treat any medical or neurologic conditions that may be responsible for the psychosis (Table 1). A study of 300,000 patients treated in the California mental health system found that 45% had an active physical disease, but fewer than half of those diseases were recognized in the mental health facility.<sup>20</sup> However, presence of a medical or neurologic disorder does not preclude the possibility of a comorbid psychiatric disorder.

### Bipolar Disorder Versus Schizoaffective Disorder

The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)* delineates diagnostic criteria for bipolar disorder and schizoaffective disorder (Table 2). The difference between these conditions can be difficult to discern, as there is considerable overlap in phenomenology (as defined by *DSM-IV-TR*).<sup>21</sup> This overlap contributes to the lack of consensus regarding diagnostic boundaries.<sup>10,22,23</sup> Schizophrenia, schizoaffective disorder, and bipolar disorder may exist along a continuum rather than as discrete entities.<sup>23</sup> Thus, it is possible to talk about a primary mood disorder with psychotic features (bipolar disorder), and a primary psychotic disorder with mood features (schizoaffective disorder).

The nomenclature is not merely academic; it also has practical implications. Patients with bipolar disorder misdiagnosed as schizoaffective disorder are less likely to receive adequate mood-stabilizing medications and therefore may be more at risk for an accelerated rate of cycling than patients who are accurately diagnosed and appropriately treated.<sup>23</sup> Conversely, patients with schizoaffective disorder misdiagnosed as bipolar disorder may stop using their antipsychotic medication as their psychosis resolves—potentially increasing the risk for a repeat psychotic episode.

**Table 1.**  
Nonpsychiatric Disorders That Can Present With Psychosis

#### Neurologic

- Head trauma
- Cranial bleed
- Brain tumors
- Dementia
- Parkinsonism
- Multiple sclerosis
- Temporal lobe epilepsy
- Stroke

#### Endocrine

- Thyroid disorder
- Diabetes
- Cushing syndrome
- Postpartum psychosis

#### Metabolic

- Vitamin B (eg, thiamine, vitamin B<sub>12</sub>) deficiency
- Hyponatremia
- Hepatic encephalopathy
- Uremia
- Hyperadrenalism
- Acute intermittent porphyria
- Nutritional deficiency
- Low serum proteins

#### Infectious Diseases

- Central nervous system infections
- AIDS
- Urinary tract infection (especially in the elderly)
- Encephalitis
- Syphilis (later stages)
- Meningitis

#### Medication Side Effects

- Antidepressants
- Corticosteroids/anabolic-androgenic steroids
- Cyclosporine
- Levodopa
- Stimulants
- Procarbazine
- Thyroxine
- Iproniazid, isoniazid
- Sympathomimetic medications
- Chloroquine
- Baclofen
- Alprazolam
- Captopril
- Anticholinergics
- Antiarrhythmics
- Antihistamines
- Antivirals

#### Substance Abuse

- Alcohol
- Drugs
- Nicotine (rare)
- Caffeine (rare)

#### Other

- Electrolyte imbalance
- Postsurgical psychosis
- Systemic lupus erythematosus
- Anemia
- Hypercalcemia or hypocalcemia
- Wilson disease
- Toxic substances

Courtesy Roger S. McIntyre, MD.

### Depressive Psychosis

The significance of the depressed phase of bipolar disorder is severely underestimated.<sup>24</sup> Depressive psychosis is more common than is generally realized, but its nosologic status is unresolved.<sup>25</sup>

### Diagnosing Ms B and Mr E

Ms B has no history of psychosis. Her psychotic symptoms are mood-congruent, and the content of her psychosis is consistent with the thematic content of manic delusions (inflated worth, sense of power) and of behaviors commonly associated with mania (sleeplessness, hypersexuality, agitation). She has a history of depression and of antidepressant-induced hypomania, and a family history of affective disorders (depression). Her activities are goal-directed, both sexually and in her attempts to help the homeless. She appears to have a primary mood disorder with psychotic features, and her diagnosis is likely bipolar disorder, though only observation while in the hospital and extended follow-up will confirm or rule out that diagnosis. We will return to Ms B and outline her treatment plan at the end of this monograph.

**Table 2. DSM-IV-TR Diagnostic Criteria for Schizoaffective Disorder and Bipolar Disorder**

**Schizoaffective Disorder**

- Uninterrupted period of illness that includes a major depressive, manic, or mixed episode
- 2 or more symptoms during a 1-month period
  - Delusions
  - Hallucinations
  - Disorganized speech
  - Grossly disorganized or catatonic behavior
  - Negative symptoms
- Delusions or hallucinations for at least 2 weeks in the absence of prominent mood symptoms
- Mood symptoms during illness
- Symptoms not attributable to substance or medical condition

**Bipolar Disorder**

- Distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week
- 3 or more symptoms present to a significant degree
  - Inflated self-esteem or grandiosity
  - Decreased need for sleep
  - Excessive talkativeness
  - Flight of ideas, racing thoughts
  - Distractibility
  - Increased goal-directed activity (socially, at work/school, or sexually); psychomotor agitation
  - Excessive involvement in pleasurable activities with potentially painful consequences
  - Symptoms do not meet the criteria for a mixed episode
  - Impairment in occupational or social functioning, relationships
  - Need for hospitalization
  - Psychotic features
  - Symptoms not attributable to substance or medical condition

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By contrast, Mr E has always displayed mood-incongruent psychotic symptoms, such as delusions of persecution and socially inappropriate behavior, which exist apart from his cycling moods. His mother reports that he displays consistent paranoid ideation, even during “normal” times when he is “neither up nor down.” He has a family history of schizophrenia. Although he talks about “building a spaceship,” he is not goal-directed. He appears to have a primary psychotic disorder with periodic mood symptoms. Once again, only careful observation of the patient, both during his hospital stay and after discharge, will enable the clinician to assess the accuracy of the diagnosis. Since this monograph focuses on bipolar disorder, and Mr E’s diagnosis is more likely to be schizoaffective disorder, we will not follow up on his treatment plan in this monograph.

**Diagnostic Workup**

The diagnostic workup has several components.

**Immediate Emergency Assessment**

Patients should immediately be assessed for risk of harm to themselves or others, severity of illness, presence or absence of social support, impaired judgment, complicating medical conditions, and lack of response to outpatient treatments (if relevant). If any of these are present, the patient should be hospitalized.<sup>26</sup>

**Interviewing the Patient and Family/Friends**

Arguably, the most important part of the diagnostic process is the interview with patient and family. The clinician starts by listening to the patient’s concerns, even if they are inadequately articulated, and to the concerns of the family. The content of psychotic thinking and behavior can sometimes provide a clue to the diagnosis.<sup>27</sup> When interviewing, the clinician should observe the patient’s affect and demeanor. Symptoms such as blunted affect, alogia, apathy, and anhedonia may be more severe in patients with schizophrenia than in those with psychotic mania or mixed mania.<sup>27</sup> A series of diagnostic questions is presented in **Table 3**.

**Table 3. Interviewing Patient and Family**

- Listen to patient’s unprompted presenting complaints
- Ask open-ended, nonleading questions
- Ask about specific symptoms of depression and mania, including how long the symptoms have been present during the current episode, how long they lasted during previous episodes (if applicable), and whether they have caused problems in social relations or work
- Always ask about suicidal ideation
- Ask about psychotic symptoms
- Consider using a screening instrument, such as the Mood Disorder Questionnaire
- Ask about family history of psychiatric illness, especially bipolar disorder
- If possible, ask patient to provide prospective mood ratings; assess when patient-rated symptoms are in the manic or hypomanic range

SOURCE: Adapted from Yatham et al. *Bipolar Disord.* 2005;7(suppl 3):5-69.

### **Screening Instruments**

The Mood Disorders Questionnaire,<sup>28</sup> the Brief Bipolar Disorder Symptoms Scale, and other screening instruments can be extremely helpful in assessing the severity of symptomatology and assembling the pieces of the diagnostic puzzle.<sup>29</sup>

### **Physical Examination**

The purpose of the physical examination is to identify or rule out any medical causes of psychosis or medical comorbidities. Because of the frequent overlap between psychiatric and neurologic symptoms, a neurologic workup should be included in the physical examination. If the patient's neurologic findings are abnormal, a computed tomography or magnetic resonance imaging scan can be used to assess and rule out any suspected neurologic basis.<sup>30</sup> Laboratory tests include complete blood cell count, electrolytes, renal and thyroid function, and toxicology screen. For at-risk patients, other tests include electrocardiogram, hepatitis C, and HIV serotyping. When diabetes or a prediabetic condition is suspected, a fasting blood glucose test is also appropriate. Females of reproductive age may require a pregnancy test. Serum levels of lithium, valproic acid, and carbamazepine should be assessed if the patient is already taking these agents.<sup>31</sup>

## **TREATING BIPOLAR PSYCHOSIS: THE NEED FOR EARLY INTERVENTION**

Early intervention is generally regarded as critical in both first- and subsequent-episode mania.<sup>32</sup> A study of patients with first-episode psychosis due to an array of psychiatric conditions found that longer delay between symptom onset and treatment may be associated with poorer outcomes<sup>33</sup>: more suffering and life disruption,<sup>34</sup> worse overall functioning, remission delay,<sup>35</sup> cognitive deficits, suicide risk, and relapse.<sup>32</sup>

## **PHARMACOLOGIC TREATMENT OF BIPOLAR PSYCHOSIS**

Pharmacologic treatment of bipolar disorder was considerably simpler when only a few agents were available. In cases of psychotic mania, conventional antipsychotic agents (eg, haloperidol) were often used, despite significant side effects. Sedatives were used as needed for agitation. Otherwise, the cornerstone of treatment of bipolar disorder was lithium.<sup>36</sup> Today, there is a panoply of efficacious agents. Selecting and sequencing these agents and incorporating them into an overall treatment plan can challenge the clinician.

The primary agents used to treat bipolar psychosis over the short term are the atypical antipsychotics (AAPs). While lithium or anticonvulsants are effective in the treatment of mania, severe mania with psychosis should be treated with combination therapy that includes an AAP. Combination therapy is often continued long term to prevent recurrence.

### **Lithium**

Since receiving FDA approval in 1971, lithium has become the standard against which newer psychotropic medications are judged regarding their potential mood-stabilizing effects.<sup>37</sup> Lithium, which is recommended in numerous guidelines as first-line acute pharmacologic treatment for mania,<sup>38</sup> has a variety of effects: antisuicidal, antimanic, antiaggressive, antidepressive, and antipsychotic.<sup>39</sup> Evidence from a

meta-analysis of 301 trials of lithium supports a role for the medication as a first-line mood stabilizer in the treatment of bipolar disorder.<sup>40</sup>

In addition to its efficacy in treating acute episodes, lithium has prophylactic value and plays a significant role in maintenance therapy after resolution of acute mania when taken on a continuous, long-term basis.<sup>41</sup> In fact, lithium is the most thoroughly studied drug for bipolar maintenance therapy.<sup>42</sup> Analyzing 5 randomized, placebo-controlled trials (770 participants), Geddes et al found lithium more effective than placebo in preventing all relapses and manic relapses, though the protective effect of lithium on depressive relapses was smaller.<sup>36</sup> These findings replicate those of numerous other studies, in which the efficacy of lithium was less robust in the treatment of dysphoric or mixed symptoms than in the treatment of manic symptoms.<sup>9,42,43</sup> Lithium also appears to exert an antisuicidal effect in bipolar disorder<sup>44</sup>; its discontinuation may be associated with a rebound increase in suicidality, above baseline levels.<sup>42</sup>

### **Divalproex**

Divalproex sodium, the FDA-approved form of valproate/valproic acid for the treatment of mania,<sup>9,45</sup> has been shown to be effective in both acute and prophylactic treatment of bipolar disorder and may have particularly antimanic or mood-stabilizing effects in bipolar patients with rapid cycling, dysphoric or mixed mania, and neurologic abnormalities.<sup>46</sup> In a meta-analysis of 10 randomized, controlled trials comparing valproate with other interventions in mania, researchers found that valproate was more efficacious than placebo; there was no significant difference between valproate and lithium, or between valproate and carbamazepine.<sup>47</sup> However, despite its common use and frequent recommendation as maintenance therapy, divalproex has not been approved by the FDA for this indication.<sup>42</sup>

### **Atypical Antipsychotics**

In the past, first-generation antipsychotics were used primarily for rapid arrest of psychosis and agitation secondary to psychosis during periods of mania.<sup>37</sup> However, some practice guidelines have advocated against their use because of their negative side-effect profile, particularly extrapyramidal symptoms (EPS) and tardive dyskinesia. Currently, so-called second-generation (atypical) antipsychotics are preferred because they usually have a lower incidence of EPS and other adverse effects. Compared with conventional agents, they are also associated with fewer emergency department visits.<sup>48</sup>

Only during the past 6 years have AAPs been FDA-approved for the treatment of bipolar mania. A substantial amount of data from randomized, controlled trials demonstrates the efficacy of AAP monotherapy in the treatment of acute mania. Perlis et al conducted a meta-analysis of 18 trials involving a total of 4304 subjects (including 1750 placebo-treated subjects) with bipolar mania—12 randomized, placebo-controlled trials of the 5 AAPs, plus 6 placebo-controlled adjunctive therapy trials.<sup>49</sup> They found that aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone all demonstrated significant efficacy in monotherapy. They also reported that add-on therapy with AAPs confers an additional benefit versus monotherapy with a traditional mood stabilizer.<sup>49</sup> According to a literature review covering the period 1990–2002, the evidence most strongly supports the efficacy and safety of olanzapine and risperidone combined with mood stabilizers in treatment of acute bipolar mania.<sup>50</sup>

One of the attractions of AAPs is an onset of action that tends to be more rapid than that of mood stabilizers, such as lithium and divalproex.<sup>51</sup> Earlier onset of action is critical in acute manic episodes, as patients are often highly agitated and aggressive. American Psychiatric Association (APA) guidelines recommend antipsychotics as first-line therapy in the treatment of acute mixed or manic bipolar episodes—used either in combination with a mood stabilizer (for severe illness) or as monotherapy (for milder illness).<sup>52</sup> AAPs in lower doses tend to be more feasible as augmentation than as monotherapy.<sup>53</sup> Representative trials supporting use of these agents are summarized below.

### **Olanzapine**

Olanzapine was the first AAP to receive FDA approval for treatment of bipolar mania (in 2000)<sup>54</sup> and has been the most widely studied of all first-line AAPs for the treatment of bipolar disorder.<sup>55</sup> Comparing the efficacy and safety of olanzapine with placebo for the treatment of acute bipolar mania in 115 patients over a 4-week period, Tohen et al found that olanzapine-treated patients had a statistically significant increased mean improvement in Young Mania Rating Scale (YMRS) scores 1 week after randomization, and this improvement was maintained throughout the study.<sup>56</sup> In addition, olanzapine-treated patients had higher response rates, though they also had statistically significant increased mean weight gain and more treatment-emergent somnolence.

Tohen et al also conducted a double-blind study comparing olanzapine with haloperidol in 177 patients with bipolar-type schizoaffective disorder over a 6-week period.<sup>57</sup> They found that olanzapine was significantly more effective than haloperidol in reducing symptoms of depression and improving cognitive symptoms. Olanzapine appears effective in reducing symptoms of mania and is well tolerated in patients with rapid cycling<sup>58</sup>; however, despite the initial favorable response, the long-term clinical outcome is less favorable in patients with rapid cycling.<sup>55,59,60</sup>

Olanzapine shows efficacy in maintenance therapy, though its adverse effects make it less desirable for long-term use.<sup>9</sup> Tohen et al compared the efficacy of olanzapine and lithium in prevention of mood episode relapse in bipolar patients with a history of mania.<sup>61</sup> They began with a 6- to 12-week open-label phase, in which all patients received olanzapine and lithium, and then continued with a 52-week double-blind, placebo-controlled trial in which patients were randomized to receive either olanzapine ( $n = 217$ ) or lithium ( $n = 214$ ). Depression relapse occurred in 15.7% of olanzapine-treated patients versus 10.7% of lithium-treated patients. However, compared with lithium, olanzapine had a significantly lower risk for manic and mixed episode relapse.

### **Risperidone**

Risperidone has a rapid antimanic effect, as shown by Hirschfeld et al, who evaluated the efficacy and safety of risperidone monotherapy versus placebo in 259 subjects over a 3-week period.<sup>62</sup> They found improvement in mean YMRS total score and other ratings to be significantly increased at end point in the risperidone group versus the placebo group, with significant between-group differences emerging soon after the start of treatment. Similar findings were obtained during a 9-week, open-label extension trial.<sup>63</sup> A review of 6 randomized trials and 6 observational studies of risperidone treatment of bipolar mania found the medication effective in the treatment of acute bipolar mania in adults with moderately severe mania.<sup>64</sup> Khanna et al found risperidone efficacious in patients with severe mania as well.<sup>65</sup>

Although no randomized, controlled trials of risperidone in long-term maintenance therapy have been reported, information about the efficacy of this medication in long-term treatment can be gleaned from open-label studies.<sup>65</sup> For example, Vieta et al conducted an open trial of 96 acutely manic bipolar patients.<sup>66</sup> For the 80 study completers, risperidone produced highly significant improvements on all efficacy measures, from weeks 1 and 4 onward, for the full 6 months. There was a significant increase in EPS by week 4, but these symptoms decreased significantly by the 6-month end point. Risperidone did not induce depressive symptoms. In fact, mean Hamilton Depression Rating Scale (HAM-D) scores improved, and exacerbation of mania was rare.

### **Quetiapine**

A 12-week randomized, double-blind, placebo-controlled trial compared the efficacy and tolerability of quetiapine and lithium in the treatment of bipolar I disorder (manic episode). The researchers found quetiapine to be superior to placebo and equivalent to lithium on the primary efficacy measure (change in YMRS score from baseline).<sup>67</sup> In another 12-week trial ( $N = 302$  patients), quetiapine was found superior to placebo in YMRS score and superior to haloperidol in adverse effects, specifically EPS.<sup>68</sup>

In a recent review of randomized, controlled trials, efficacy and tolerability of quetiapine were evaluated in the acute and maintenance phases of bipolar disorder. In trials involving patients with mania, quetiapine was as effective as adjunctive therapy when combined with lithium or valproate.<sup>69</sup> Suppes et al added quetiapine to ongoing treatment of bipolar I outpatients ( $N = 15$ ) for symptoms of illness, such as mood lability.<sup>70</sup> Prospectively obtained evaluations showed improvement in the majority of patients.

### **Ziprasidone**

In the treatment of acute mania, fewer data are available for ziprasidone than for olanzapine, risperidone, and quetiapine. Nevertheless, data for ziprasidone are encouraging; they demonstrate that this medication can be useful in the treatment of bipolar mania.<sup>55</sup>

Studying 210 patients randomized to receive ziprasidone or placebo over a 3-week period, Keck et al found that ziprasidone produced rapid, sustained improvement relative to baseline and placebo on all primary and most secondary efficacy measures.<sup>71</sup> Significant improvement was typically observed within 2 days after treatment initiation, and was maintained over the entire study period. Conducted in 2005, a 4-year review of the medication found it to be efficacious over the short term and the long term, and as an augmenting agent in the acute treatment of mania, with sustained efficacy up to 1 year.<sup>72</sup> In trials, ziprasidone was well tolerated by patients with bipolar disorder and did not increase weight or glucose and lipid levels.<sup>73</sup>

### **Aripiprazole**

A review of aripiprazole found that it had rapid onset of action (as early as day 4) and was effective in treating patients with bipolar I disorder experiencing an acute manic or mixed episode.<sup>74</sup> The medication was significantly more effective than placebo in improving manic symptoms in 3-week placebo-controlled trials, and its effectiveness (response rate 50%) was superior to that of haloperidol (28.4%) in a 12-week comparative trial. Time to relapse of symptoms in stabilized patients with bipolar I disorder who previously experienced a manic episode was significantly longer with aripiprazole than with placebo in a 26-week

relapse prevention study.

A recent 3-week, placebo-controlled study randomized 272 hospitalized patients with acute manic or mixed episodes of bipolar I disorder to receive aripiprazole or placebo.<sup>75</sup> Compared with placebo-treated patients, patients in the treatment group showed significantly more improvement from baseline as early as day 4, and this improvement was maintained through week 3.

Aripiprazole has demonstrated efficacy in maintenance therapy. Keck et al found aripiprazole superior to placebo in deferring time to relapse in patients with a recent manic or mixed episode.<sup>76</sup>

### **Clozapine**

Clozapine has shown efficacy for patients with acute mania and psychosis—especially when treatment resistance, intolerance of other medications, and rapid-cycling bipolar disorder are involved. Barbini et al found that clozapine combined with lithium was rapidly efficacious in ameliorating symptoms of acute mania in 30 hospitalized patients.<sup>77</sup> In an open-label study, Green et al examined the efficacy of clozapine over a 12-week period in the treatment of 22 patients with treatment-refractory bipolar disorder and active manic and psychotic symptoms.<sup>78</sup> Significant improvement was noted in YMRS scores and in other rating scale scores. Reviewing studies on use of clozapine in disorders presenting with psychosis, Zarate et al found that patients having manic or psychotic phases of schizoaffective or bipolar disorder were significantly more likely to respond to clozapine than were patients with schizophrenia or severe depressive syndromes.<sup>79</sup> Clozapine, however, is associated with several serious toxic reactions, including agranulocytosis, seizures, and cardiorespiratory complications,<sup>80</sup> making it an appropriate choice only for more treatment-resistant patients. Clozapine might also have utility in maintenance therapy with treatment-resistant patients.<sup>9</sup>

### **Comparative Trials**

Few trials have compared the efficacy of various AAPs in the treatment of acute mania. Baker et al compared olanzapine (n = 165) and risperidone (n = 164) in the treatment of bipolar mania over a 3-week period.<sup>81</sup> They found no significant differences between olanzapine and risperidone in YMRS scores. However, in another study olanzapine-treated patients showed increased improvements on the Montgomery-Asberg Depression Rating Scale and on the Clinical Global Impression Rating Scale (CGI).<sup>82</sup> Petrie compared risperidone and olanzapine as adjuncts to lithium or divalproex in 37 patients with an acute manic or mixed episode over an 8-week period.<sup>82</sup> These agents were similarly effective, according to YMRS, CGI, and Brief Bipolar Rating Scale scores. However, patients treated with the risperidone–lithium/divalproex combination had significant HAM-D improvements versus patients treated with the olanzapine combination.

In a meta-analysis, Perlis et al noted that most studies of combination therapy have focused on antipsychotic agents added to mood stabilizers, rather than on mood stabilizers added to antipsychotic agents.<sup>49</sup> The fact that patients already experience some improvement with a mood stabilizer tends to bias results toward less benefit with combination therapy.

### **Anticonvulsant Mood Stabilizers**

Use of novel antiepileptic medications has become increasingly common in the treatment of bipolar disorder over the past decade.<sup>83</sup>

These agents include carbamazepine, oxcarbazepine, lamotrigine, topiramate, gabapentin, tiagabine, and zonisamide. Valproate, also an anticonvulsant, was discussed earlier.

### **Carbamazepine**

Like valproate, carbamazepine was first developed more than 30 years ago for the treatment of epilepsy.<sup>84</sup> Subsequent studies showed the efficacy of carbamazepine in the treatment of acute mania and suggested efficacy as maintenance therapy in bipolar disorder. Carbamazepine has been in use for many years, and its utility is well established. This medication is considered equal to valproate in efficacy; however, valproate may be more tolerable for short-term use, while carbamazepine may be better suited for long-term therapy. Common adverse effects (somnolence, nausea, vomiting) usually diminish over time. Carbamazepine has no impact on weight.<sup>85</sup> This agent is not considered generally efficacious in treating bipolar depression,<sup>86</sup> but it has been found to significantly increase mean time to relapse after a manic or mixed episode, as compared with placebo.<sup>87</sup>

Extended-release carbamazepine is FDA-approved as monotherapy in treating acute bipolar manic and mixed episodes.<sup>88</sup> Pooled data from 2 identically designed 3-week randomized, double-blind, placebo-controlled trials involving 443 adult patients found extended-release carbamazepine to be superior to placebo, based on significant improvements in mean YMRS scores.

### **Oxcarbazepine**

Oxcarbazepine is structurally similar to carbamazepine, but there are relatively few rigorously controlled trials supporting its efficacy in the treatment of bipolar disorder.<sup>9</sup> According to a review of articles and studies from 1950 to 2005, oxcarbazepine may be efficacious in treating acute mania, may be a useful adjunctive therapy in bipolar disorder prophylaxis and in treating acute bipolar depression, and is generally well tolerated.<sup>89</sup> However, in a recent trial involving 116 children and adolescents (ages 7–18) with manic or mixed bipolar I disorder, oxcarbazepine did not significantly improve YMRS scores at end point, compared with placebo, and 5% of patients in the treatment group experienced dizziness, nausea, and other adverse symptoms—an incidence at least twice that of the placebo group.<sup>90</sup>

### **Lamotrigine**

Lamotrigine is FDA-approved for maintenance treatment of bipolar I disorder.<sup>91</sup> It has been found efficacious in the treatment of acute bipolar I depression and in long-term prevention of recurrent mood episodes after an acute-illness phase in bipolar I disorder.<sup>92</sup> Several studies have found lamotrigine more effective than placebo in delaying time to relapse or recurrence of a mood episode,<sup>91–93</sup> though it has been more effective against depressive episodes than against manic episodes.<sup>94</sup> However, a recent post hoc efficacy analysis of two 18-month placebo-controlled maintenance trials of lamotrigine showed that it protected against any mood episode recurrence in bipolar I disorder.<sup>95</sup> Goodwin et al conducted a pooled analysis of 2 clinical trials comparing lamotrigine, lithium, and placebo in the treatment of bipolar I disorder in 1315 recently depressed or manic patients.<sup>96</sup> They found both agents superior to placebo in delaying time between intervention and any mood episode, with lamotrigine more effective against depression, and lithium more effective against mania. Lamotrigine has been found to be more

efficacious than placebo in preventing depression, regardless of the direction (manic or depressive) of the index episode.<sup>42</sup>

Unlike divalproex, lamotrigine cannot be given in a loading dose but must be started at a low dose (usually 25 mg/d) and slowly escalated to avoid the risk for serious rash, including Stevens-Johnson disease.<sup>97</sup> Metabolic interactions with carbamazepine and valproate must be considered when determining starting dose and titration of lamotrigine.

### Topiramate

Topiramate is generally not recommended for treatment of acute mania, as this medication has failed to demonstrate antimanic efficacy in randomized controlled trials.<sup>4</sup> A meta-analysis found insufficient evidence to recommend use of topiramate in any phase of bipolar illness, as either monotherapy or adjunctive treatment.<sup>98</sup> However, topiramate may have some utility for treatment of bipolar disorder with comorbid binge eating and obesity,<sup>99</sup> and in attenuating or reversing weight gain induced by AAPs.<sup>4</sup> Topiramate, it should be noted, carries a dose-dependent risk for metabolic acidosis.<sup>100</sup>

### Other Anticonvulsants

Gabapentin and tiagabine are not generally recommended for treatment of acute mania.<sup>4</sup> Gabapentin may be useful in the treatment of comorbid panic disorder or alcohol abuse<sup>4</sup> or anxiety disorders.<sup>101</sup> In 2 recent meta-analyses, there was insufficient evidence to recommend tiagabine for acute or maintenance treatment of bipolar disorder.<sup>102,103</sup> Very few studies have been conducted on zonisamide, another anticonvulsant, and findings have been mixed: improvement in depressive symptoms (in a recent 8-week open-label study)<sup>104</sup> and worsening mood symptoms leading to a high discontinuation rate (in another study).<sup>105</sup>

### Benzodiazepines

This class of medications is used in bipolar mania on an adjunctive basis to control insomnia, agitation, and anxiety.<sup>4</sup> Given their increased therapeutic effects and more rapid onset of action, high-potency benzodiazepines (alprazolam, clonazepam, lorazepam) have replaced low- and medium-potency benzodiazepines.<sup>106</sup> However, because of serious concerns about medication dependence, benzodiazepines are recommended as adjunctive therapy rather than as primary agents for mania.<sup>4</sup>

## SELECTING AND SEQUENCING PHARMACOLOGIC AGENTS: CONSENSUS GUIDELINES AND ALGORITHMS

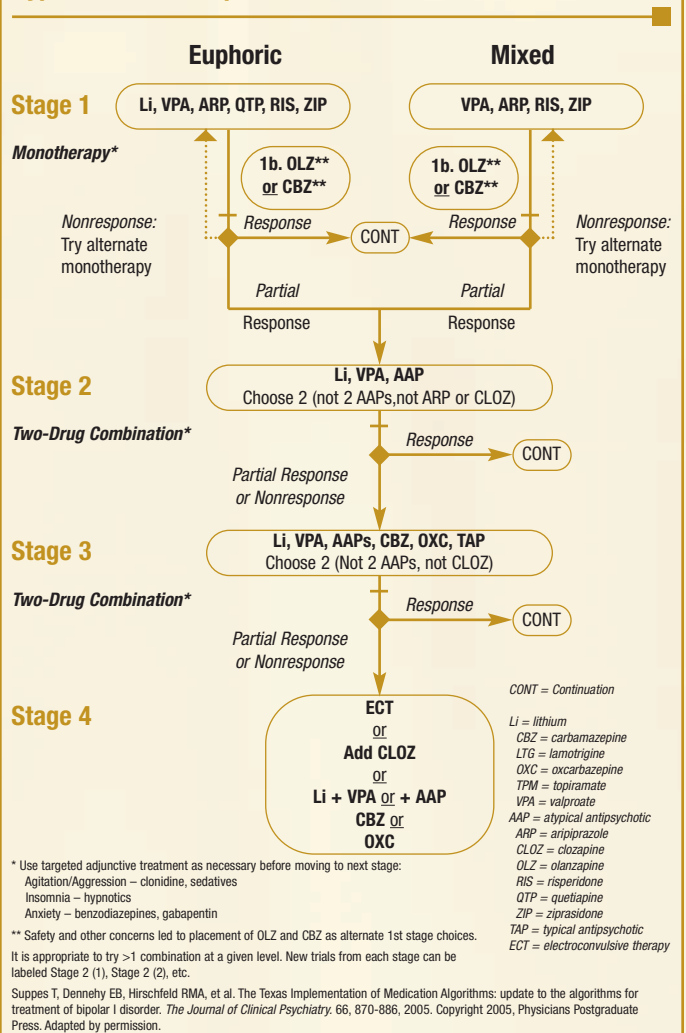
Treatment decisions in psychiatry, especially for a condition as complex as bipolar disorder, must take into account several variables, including symptom severity, past treatment history, patient preference, medication tolerability, and clinical response.<sup>107</sup> Many clinicians do not systematically assess or measure the complex array of factors involved in bipolar disorder and instead often rely on memory and general impressions when making treatment decisions.<sup>108</sup> Given the number of agents available, clinicians should have guidance in selecting and sequencing medications. Treatment algorithms and expert guidelines, presenting evidence supporting or refuting use of a given medication or combination therapy, can be helpful in clinical decision-making.<sup>109</sup> Clinicians should keep in mind that no guidelines can fully address the complexities involved in providing care for a particular patient. Sound judgment, based on clinical

experience, should be used in applying recommendations.<sup>9</sup>

There are several sets of expert guidelines, including American Psychiatric Association (APA),<sup>52</sup> the Expert Consensus Guideline Series (Medication Treatment of Bipolar Disorder<sup>110</sup> and Treatment of Behavioral Emergencies<sup>111</sup>), the Canadian Network for Mood and Anxiety Treatments (CANMAT),<sup>4</sup> and the Texas Medication Algorithm Project (TMAP).<sup>9</sup> Compared with other therapeutic regimens, treatment guided by TMAP algorithms has been associated with increased initial and sustained improvement in measures of mania and psychosis.<sup>112</sup> According to Texas Implementation of Medication Algorithms (TIMA), a clinician treating a patient should choose an agent that has the most evidence supporting its efficacy and safety—but also, when possible, an agent that has proved effective with the patient in the past.<sup>9</sup> Although clinicians are encouraged to move through agents linearly, treatment should be based on which agent is most likely to be tolerated, and on patient preference, even if this means moving to a more advanced algorithm stage, with the possibility of subsequent backtracking. The goal of treatment should be symptom remission.

The algorithm is a stepwise approach to treatment, organized by stages (Figure). Within each treatment stage, medical decisions should be based on 4 factors: efficacy (symptom improvement), tolerability (side effects), safety, and serum concentrations (as applicable).<sup>9</sup>

**Figure. Algorithm for Treatment of Bipolar Disorder – Hypomanic/Manic Episode**



## CREATING A PHARMACOLOGIC MAINTENANCE PLAN

Maintenance pharmacotherapy is recommended for all patients with bipolar disorder who have had at least one moderately severe manic episode.<sup>4</sup> After the psychosis has resolved and the patient has begun to stabilize, the clinician can initiate the maintenance plan, which usually involves simplifying the medication regimen or transitioning to a treatment with the best documented efficacy and tolerability for maintenance therapy.<sup>9</sup> Attempts to simplify the regimen should not be made until several weeks have passed; if a medication is discontinued, it should be tapered slowly, usually by no more than 25% a week.<sup>4</sup> When a switch in medications is needed, the clinician should slowly and simultaneously titrate the current one down and the new one up, unless medical necessity requires rapid discontinuation.<sup>9</sup>

Maintenance therapy is intended to improve overall function, prevent relapse and recurrence, and reduce subthreshold symptoms, suicide risk, and cycling frequency or milder mood instability.<sup>26</sup> For the patient who refuses long-term pharmacologic maintenance therapy, the clinician should use psychosocial strategies, including clear discussion of the risks and benefits of maintenance therapy, and should continue effective acute-phase dosages for at least 3 to 6 months.<sup>4</sup> The patient should be closely monitored, and, in the event of symptom recurrence, medication should be reinstated immediately. Lithium discontinuation is often followed by recurrence, even in patients with bipolar disorder who have been stable for a prolonged period of time.<sup>4,113</sup>

For patients with a history of psychosis, clinicians should be more hesitant to discontinue antipsychotics. However, for patients with bipolar disorder (as opposed to schizophrenia), it is reasonable to taper to a low dose of antipsychotic or to consider discontinuation, and rely instead on lithium and possibly an anticonvulsant mood stabilizer. Most expert guidelines, including TIMA guidelines, recommend lithium and divalproex for long-term treatment.<sup>113</sup> However, these agents are not always sufficient, as their utility may be offset by limited response, relapse, and significant side effects. Additional agents (eg, antipsychotics) may be needed to redress some of the shortcomings of these established treatments.<sup>66</sup> TIMA guidelines regard continuation of an effective and well-tolerated acute-phase treatment, such as an antipsychotic, to be a reasonable option for maintenance treatment.<sup>9</sup> Although the role of combination treatment versus monotherapy in maintenance remains to be determined, most patients in clinical practice receive combination therapy.<sup>9</sup> More studies are needed evaluating various combinations of agents during maintenance therapy.

TIMA offers 2 alternative sets of maintenance recommendations based on the nature of the acute episode—manic or depressive.<sup>9</sup> Although some agents (eg, antipsychotics) may have equal efficacy in short-term acute episodes or in open trials of longer term maintenance, both sets of recommendations are based on the sum of the current evidence. These treatment recommendations will be revised periodically, as more controlled scientific studies and new information become available. Recommendations for maintenance therapy after a manic episode are listed in **Table 4**.

## MANAGEMENT OF ADVERSE EVENTS

Managing the adverse events associated with pharmacologic agents is an essential part of long-term maintenance. Adverse events pose potential health risks, compromise quality of life, and often lead to medication nonadherence.<sup>115</sup> A detailed list of adverse events associated

**Table 4. Texas Implementation of Medication Algorithms (TIMA) Recommendations for Maintenance Treatment After Severe Acute Episode of Mania\***

### Level 1

- Lithium or valproate
- Lamotrigine (to prevent new depressive symptoms)
- Olanzapine

### Level 2

- Aripiprazole

### Level 3

- Carbamazepine
- Clozapine (for treatment-resistant patients)

### Level 4

- Quetiapine
- Risperidone
- Ziprasidone

### Level 5

- Typical antipsychotics
- Oxcarbazepine
- Electroconvulsive therapy

\*Levels are based on amount of evidence for each intervention and are in order of preferability.

Adapted in abbreviated form from Suppes T, Dennehy EB, Hirschfeld RM, et al. *J Clin Psychiatry*. 2005;66:870-886.

with most major medications used to treat bipolar disorder appears in **Table 5** and **Table 6**. Here is a discussion of the most common concerns and side effects.

### Metabolic Side Effects

Metabolic side effects of antipsychotic treatment include weight gain and dyslipidemia, with increased susceptibility to diabetes and cardiovascular disease.<sup>115</sup> Some psychiatrists may not perform sufficient metabolic screening for these conditions in patients taking antipsychotics.<sup>116</sup> Nevertheless, monitoring for these effects falls within the purview of psychiatric practice—though treatment is generally provided by specialists in the appropriate disciplines (eg, endocrinologists, cardiologists). The psychiatrist should facilitate patient access to general medical care and collaborate with any other specialists involved in the patient's treatment.

The mechanisms responsible for the weight gain associated with AAPs are unknown.<sup>117</sup> One hypothesis is that these medications alter the hunger and satiety mechanisms. Weight gain and changes in body composition may account for the metabolic complications associated with antipsychotic therapy—insulin resistance, prediabetes/diabetes, and dyslipidemia. Insulin action is impaired (insulin resistance) either by the increase in weight or by a direct effect of the medication on insulin-sensitive target tissues. In addition, evidence suggests that changes in serum lipids are concordant with changes in weight. Clozapine and olanzapine, which produce the most weight gain, are associated with the largest increases in total cholesterol, low-density lipoprotein cholesterol, and triglycerides and with decreased high-density lipoprotein cholesterol. These changes—insulin resistance, dyslipidemia, and obesity—comprise the metabolic syndrome and are a risk factor not only for diabetes but also for cardiovascular disease.<sup>118</sup>

**Table 5. Relative Adverse Effect Profiles of Atypical Antipsychotics**

Adverse Effect	Atypical Antipsychotic				
	Olanzapine	Risperidone	Quetiapine	Ziprasidone	Aripiprazole
Weight gain	High	Moderate	Moderate	Low to none	Low to none
Dyslipidemia	High	Low	Low	None	None
Glucose dysregulation	Moderate	Low	Low	None	
Sedation	High	Moderate	High (during titration phase)	Low	Low
Extrapyramidal symptoms	Low	Moderate	None	Low	Low
QTc prolongation	Low to none	Low to none	Low	Low*	Low
Prolactin elevation	Low to none	Moderate	None	None	None
Mania induction	Low to none	Low to none	Low to none	Low to none	Low to none
Anticholinergic symptoms (eg, dry mouth, constipation)	Moderate	Low	Low	Low	Low

\*Except in high-risk patients

SOURCE: Adapted from Ehret MJ, Levin GM. *Pharmacotherapy*. 2006;26:1134-1147.

Comprehensive evaluation of patients with bipolar disorder should include an assessment of medical and behavioral factors associated with obesity and diabetes. Patients should be assessed on exercise habits, eating patterns, comorbid binge-eating disorder, bulimia nervosa, caffeine dependence, smoking, and thyroid dysfunction.<sup>118</sup> Patients starting treatment with antipsychotics should be screened at baseline, and then monitored regularly. Baseline and ongoing monitoring recommendations are listed in **Table 7**.

Strategies to manage weight gain include adjunctive therapy with medication such as amantadine, histamine (H<sub>2</sub>) antagonists, metformin, topiramate, and orlistat.<sup>119</sup> Switching from one medication to another in the same class is also an alternative. Compared with aripiprazole and ziprasidone, olanzapine appears to have a significantly higher risk for metabolic effects,<sup>120</sup> while among patients with schizophrenia or schizoaffective disorder, risperidone appears to have a significantly lower cardiovascular risk than olanzapine or clozapine.<sup>121</sup>

Behavioral interventions can help patients stop weight gain and lose weight over time, and dietary interventions appear promising.<sup>122</sup> Patients should be given information before they come in for office visits, and discussions about weight management should be documented in their charts.<sup>123</sup> Patient education, discussed more fully later in this monograph, is critical.

### Extrapyramidal Symptoms

Although AAPs have a low propensity for causing EPS, they are not risk-free.<sup>115</sup> Ghaemi et al reviewed 51 individual-patient trials of AAPs and found that more than half of a variety of patients experience EPS in this “real-world” setting—a rate much higher than the 5% to 15% reported in clinical trials.<sup>124</sup> Yet EPS may be difficult to recognize and misinterpreted as signs and symptoms of psychotic illness.<sup>125</sup> EPS can include active movement disorders (parkinsonism, acute akathisia, acute dystonia) and chronic movement disorders (tardive dystonia, chronic akathisia, tardive dyskinesia).<sup>125</sup> Symptoms include neck and spine movements, gait and walking disorders, oral and facial symptoms, finger movements, limb movements, eye symptoms, and difficulties with

vocalization, breathing, and swallowing.<sup>126</sup> The 12-item Abnormal Involuntary Movement Scale<sup>127</sup> is the most commonly used instrument for assessing tardive dyskinesia.<sup>125</sup>

These effects can be addressed by using the lowest dose possible and keeping treatment duration as short as possible (especially with elderly patients, who often respond to doses much lower than those used for younger patients).<sup>80</sup> If this approach fails, medication-induced parkinsonism and dystonia may improve with use of anticholinergics, and akathisia may improve with use of benzodiazepines or low-dose propranolol. Switching to another agent in the same class may be necessary. The need for antipsychotic therapy should be reviewed on an ongoing basis.

### Sedation and Somnolence

Sleep disturbances, which are common in psychiatric patients, are often compounded by antipsychotic medications.<sup>128</sup> Sedation can be a problem for patients who are trying to reintegrate with society and can interfere with their treatment regimen. Sedation affects younger patients, but it is especially common and problematic among the elderly. Strategies for managing sedation include eliminating other sedative agents, having the patient take as much of the antipsychotic medication as possible at bedtime, reducing the dose of the antipsychotic slowly and cautiously, and switching to a less sedating antipsychotic. In addition, the clinician should not assume that sedation is entirely the result of using antipsychotic medications. Hypothyroidism, a side effect of lithium, can also cause fatigue, and it should be evaluated.<sup>128,129</sup> Use of caffeine, bupropion, and modafinil can be considered, but stimulants should be used cautiously for this indication because of their potential for inducing or exacerbating mania.<sup>128</sup>

### Lithium and Thyroid Abnormalities

Lithium affects thyroid function by inhibiting thyroid hormone release and perhaps by altering thyroid gland texture, with hypothyroidism and goiter resulting.<sup>130</sup> In addition, patients with affective disorders have a high incidence of comorbidity with thyroid disease, even in the absence

**Table 6. Adverse Effects of Traditional Mood Stabilizers (In Descending Order of Frequency)**

Medication	Adverse Effect
Lithium	Hypothyroidism
	Polyuria, polydipsia
	Gastrointestinal disturbance
	Dose-dependent tremor
	Weight gain
	Sedation
	Memory problems
Valproic acid	Nausea
	Sedation
	Headache
	Ataxia
	Alopecia
	Weight gain
	Elevated aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase
	Dose-dependent thrombocytopenia
Carbamazepine	Pancreatitis (rare)
	Dizziness
	Syndrome of inappropriate antidiuretic hormone secretion
	Somnolence
	Nausea
	Vomiting
	Rash
	Depression
Lamotrigine	Dose-dependent bradyarrhythmias
	Dizziness
	Headache
	Nausea
	Somnolence
	Rash
	Insomnia
	Tremor
Stevens-Johnson syndrome	

SOURCE: Ehret MJ, Levin GM. *Pharmacotherapy*. 2006;26:1134-1147.

of lithium treatment. Patients should be regularly monitored (Table 8) and referred to an endocrinologist if thyroid-stimulating hormone concentrations are repeatedly abnormal or if goiter or nodules are detected. However, thyroid function abnormalities do not necessarily contraindicate lithium treatment, and there are times when lithium

treatment should be continued even after thyroid abnormalities have developed. Hypothyroidism can be treated with thyroxine supplementation.<sup>131</sup>

### Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome, a rare but life-threatening idiosyncratic reaction to a neuroleptic medication, is characterized by hyperthermia, muscle rigidity, mental status changes, and autonomic dysfunction.<sup>132</sup> This syndrome is more commonly associated with conventional antipsychotics as opposed to AAPs. For bipolar patients, concomitant use of mood stabilizers (eg, lithium) may increase susceptibility to this condition. Patients using these agents should be advised to hydrate adequately and—of critical importance—avoid becoming overheated.

### QTc Prolongation

Although modest prolongation of the QTc interval has been reported, use of AAPs appears not to be associated with an increase in cardiac events.<sup>133</sup> Evaluating the effects of 6 antipsychotic agents (haloperidol, thioridazine, ziprasidone, quetiapine, olanzapine, risperidone), Harrigan et al found that mean QTc intervals did not exceed 500 milliseconds in any patient, regardless of the presence or absence of metabolic inhibition.

### Hyperprolactinemia

Excessive prolactin can suppress ovarian and testicular function—potentially causing menstrual irregularity, breast tenderness and engorgement, infertility, headaches, reduced libido, and estrogen-deficiency symptoms in women, and reduced libido, erectile dysfunction, fatigue, and occasionally gynecomastia in men.<sup>132</sup> Risperidone has been associated with dose-dependent sustained hyperprolactinemia,<sup>132</sup> but an analysis of randomized double-blind studies of risperidone in patients with chronic schizophrenia found that a risperidone-associated increase in serum prolactin levels was not significantly associated with emergence of possible prolactin-related side effects.<sup>134</sup> Management entails reducing the dose of the antipsychotic, switching agents, or adding a dopamine agonist, such as bromocriptine or cabergoline.<sup>132</sup>

### Constipation

Constipation is a common adverse effect of some antipsychotics because of their anticholinergic mechanism of action.<sup>135</sup> In a study of binding profiles, clozapine, olanzapine, and quetiapine showed dose-dependent increases in anticholinergic activity, while aripiprazole,

**Table 7. Monitoring Patients Who Are Using Atypical Antipsychotics**

Assessment	Assessment Time						
	Baseline	4 wk	8 wk	12 wk	Quarterly	Annually	Every 5 Years
Personal/family history	x					x	
Weight (body mass index)	x	x	x	x	x		
Waist circumference	x					x	
Blood pressure	x			x		x	
Fasting plasma glucose	x			x		x	
Fasting lipid profile	x			x			x

SOURCE: American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity. *Diabetes Care*. 2004;27:599.

**Table 8. Monitoring Parameters for Traditional Mood Stabilizers**

Medication	Parameter	Monitoring Frequency (After Baseline)
Lithium	CBC count with differential	Annually
	TSH, T <sub>3</sub> , T <sub>4</sub>	TSH at 3 and 6 months, then annually
	Electrolytes	Every 3 months during titration, then every 6 months
	Specific gravity	Every 3 months during titration, then every 6 months
	BUN, S <sub>Cr</sub>	Every 6 months
	ECG (in patients >40 y)	Annually
	Pregnancy test	Baseline
	Weight, glucose	Annually
	Serum concentrations	1 week after start of therapy or dosage increase or if there is a change in symptomatology
Valproic acid	CBC count with platelet count	Every 2 months for first 6 months, then annually
	Liver function tests (ALT, AST, total bilirubin, PT, aPTT)	Every 2 months for first 6 months, then annually
	Weight	Baseline
Carbamazepine	CBC count with differential	Every 2 weeks in first month, then monthly for 3 months, then every 3 months for remainder of first year, then every 6 months thereafter
	Liver function tests	At 3 months, at 6 months, then annually
	Platelets	Every 6 months
	Electrolytes	At 3 months, at 6 months, then annually
	Serum concentrations	5 days after dosage change or sooner if toxicity or nonadherence is suspected
Lamotrigine	Hypersensitivity reaction*	

CBC indicates complete blood cell; TSH, thyroid-stimulating hormone; T<sub>3</sub>, triiodothyronine; T<sub>4</sub>, thyroxine; BUN, blood urea nitrogen; S<sub>Cr</sub>, serum creatinine; ECG, electrocardiogram; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PT, prothrombin time; aPTT, activated partial thromboplastin time.

\*Lamotrigine should be discontinued at the first sign of rash, unless the rash is clearly not medication-related, regardless of therapy duration.

SOURCE: Ehret MJ, Levin GM. *Pharmacotherapy*. 2006;26:1134-1147.

risperidone, and ziprasidone did not.<sup>136</sup> Clozapine has also been associated with high rates of constipation.<sup>137</sup> In a study performed on nursing home patients with psychotic symptoms and behavioral disturbances, risperidone was found to be less constipating than olanzapine,<sup>138</sup> and an expert consensus panel endorsed risperidone as the first choice for treating constipated elderly patients who require antipsychotic treatment.<sup>139</sup>

Constipation compromises quality of life<sup>140</sup> and can be inconvenient, but it can also become life-threatening when fecal matter becomes impacted. Pharmacotherapy includes use of tegaserod, lubiprostone,<sup>141</sup> and docusate.<sup>142</sup> Given the risks associated with long-term laxative use,<sup>135</sup> nonpharmacologic approaches are preferable. These approaches include supplementation with psyllium or another fiber<sup>135,141</sup> adequate hydration,<sup>143</sup> and biofeedback.<sup>141</sup> Patients should be informed that constipation is a potential side effect of AAPs. They should also be encouraged to take preventive nonpharmacologic measures and, if these are insufficient, to seek further medical help.

### Monitoring Patients During Maintenance Treatment

Maintenance therapy is a long-term process that requires regular follow-up. Maintenance involves ongoing monitoring of medication side effects and adjusting medications or adding adjunctive agents as necessary. As noted earlier, Table 8 lists monitoring parameters and required laboratory tests for treatment with traditional mood stabilizers.

## HANDLING MEDICAL AND PSYCHIATRIC COMORBIDITIES

There is an increased incidence of medical comorbidities among patients with affective disorders.<sup>129</sup> These comorbidities, which are often overlooked,<sup>20</sup> are associated with poorer outcomes in terms of quality of life, health, treatment response, and potential for suicide, as well as increased costs.<sup>129</sup> Using data extracted from the Canadian Community Health Survey, McIntyre et al investigated the prevalence and functional implications of comorbid general medical disorders in bipolar disorder. Of 36,984 survey completers, 938 screened positive for a lifetime manic episode; that sampling reflected 2.4% of the general population aged 15 years and older, according to study investigators, who used a household-weighted formula. Rates of chronic fatigue syndrome, migraine, asthma, chronic bronchitis, multiple chemical sensitivities, hypertension, and gastric ulcer were significantly higher in the bipolar disorder group than in the general population. These comorbidities occur at rates higher than those predicted by chance.<sup>144</sup> Many psychiatric comorbidities (eg, attention-deficit/hyperactivity disorder [ADHD]<sup>145</sup> and substance use disorder [SUD])<sup>144</sup> are also frequently missed during evaluations of patients with bipolar disorder.

### Attention-Deficit/Hyperactivity Disorder

There is much diagnostic overlap between ADHD and bipolar disorder, and these conditions may present similarly (eg, excessive talking,

distractibility, increased activity and restlessness, social disinhibition).<sup>146</sup> There are, however, notable differences. Bipolar disorder is characterized by inflated self-esteem or grandiosity, increased goal-directed activity, flight of ideas, decreased need for sleep, and increased libido. These symptoms are not associated with ADHD, and neither is psychosis. Milberger et al studied the overlap and concluded that ADHD and bipolar disorder are discrete, separate entities.<sup>147</sup> On the other hand, data from clinicoepidemiologic, family, neuropsychological, neuroimaging, and laboratory studies have been cited to support such a relationship.<sup>148</sup> In patients with both bipolar disorder and ADHD, mood disorder onset is approximately 5 years earlier, periods of wellness are shorter, and depression is more frequent than in patients with only ADHD.<sup>145</sup> Results from several studies suggest the conditions can be differentiated, despite their symptomatic overlap. Wilens et al interviewed 51 adults referred to clinical ADHD trials—24 with bipolar disorder and 27 without bipolar disorder—and found that those with comorbid ADHD and bipolar disorder have prototypic symptoms of both disorders, suggesting both are present and are clinically distinguishable.<sup>149</sup>

Research on treatment of comorbid ADHD and bipolar disorder is in its infancy. The number of randomized controlled trials is insufficient to provide robust guidance in the treatment of adults, but generally treatment begins with adequate mood stabilization; once mood has been stabilized, stimulant therapy is cautiously introduced, as stimulants can trigger mania and therefore psychotic symptoms. To remain vigilant about the return of mania, the patient can track mood symptoms in a mood diary. Biofeedback, which has shown efficacy in ameliorating ADHD symptoms and is free of side effects, can be used adjunctively or when stimulants are contraindicated.<sup>150,151</sup>

### **Substance Abuse**

SUD and psychiatric disorders are often comorbid.<sup>152</sup> A disproportionate number of substance abusers have psychiatric conditions.<sup>153</sup> In a major epidemiologic study, Grant et al<sup>152</sup> found positive and significant associations between most SUDs and independent mood and anxiety disorders; they concluded that these affective conditions, which develop independently of intoxication and withdrawal, are among the most prevalent US psychiatric disorders.

The etiology of this comorbidity is not well understood.<sup>154</sup> The several possible explanations include overlapping symptoms with resultant misdiagnosis of mood disorder; self-medication of mood symptoms; substance abuse revealing mood symptoms or triggering a mood episode; and a common genetic vulnerability. However, none of these models offers a complete explanation for all the data. Both conditions are associated with impulsivity, and people with both conditions display more impulsivity than people with either condition alone.<sup>155</sup>

Patients with comorbid SUD and bipolar disorder have one of the highest levels of unmet needs within the bipolar population. Several factors are involved, including poor treatment adherence, service provision issues, and diagnosis difficulties.<sup>156</sup> As intoxication, poor judgment, and impulsivity may deter adherence, addressing substance abuse will likely enhance adherence.<sup>154</sup>

Data from controlled studies on the pharmacotherapy of these comorbid conditions are limited. Carbamazepine,<sup>157</sup> lithium,<sup>158</sup> and valproate<sup>159</sup> have been studied in abusers of cocaine (carbamazepine) and alcohol or marijuana. Several researchers have examined use of AAPs in patients with combined SUD and bipolar disorder. Quetiapine was found effective

in reducing cocaine dependence,<sup>160</sup> and aripiprazole was found effective for patients with alcohol and cocaine addictions.<sup>161</sup> Lamotrigine has also demonstrated efficacy in reducing cocaine cravings.<sup>162</sup> Some research supports topiramate as efficacious in reducing cravings for alcohol.<sup>163</sup>

Nonpharmacologic approaches include an integrated treatment paradigm that simultaneously addresses both disorders in a comprehensive treatment program that consists of case management, motivational strategies, vocational rehabilitation services, family counseling, housing, and medication.<sup>164</sup> Although this program yielded only modest improvements in symptoms of bipolar disorder, there was significant remission from substance abuse, plus other improvements in psychosocial function. Several interventions using cognitive behavior therapy have also been useful in treating this population.<sup>154</sup>

### **Nicotine**

There is a significant relationship between smoking and a history of psychosis in patients with bipolar disorder.<sup>165</sup> Although smoking may not be as prevalent in bipolar disorder as it is in schizophrenia,<sup>166</sup> it appears to be more prevalent than in the general population.<sup>167</sup> Combinations of an AAP (olanzapine or risperidone, in particular) and a nicotine transdermal patch have been found effective in treating a schizophrenic population.<sup>168</sup> Psychiatrists and other mental health professionals should routinely ask patients about smoking status, advise them to quit, and refer them to or provide counseling, pharmacotherapy, and support services.<sup>169</sup>

## **MANAGING THE SPECIAL NEEDS OF WOMEN**

Women are particularly affected by bipolar disorder due to the interaction of reproductive events and the illness<sup>170</sup> and the treatment medications involved. Although mood disorders in general are more than 1.5 times more prevalent among women than among men,<sup>171</sup> lifetime prevalence of bipolar I disorder appears not to differ between men and women.<sup>172</sup> Women with bipolar disorder, however, are more likely to have a rapid cycling course, experience mixed episodes, experience more depressive episodes, and report more overall impairments.<sup>170,173</sup> Clinicians treating women face an array of challenges not encountered in the treatment of men.

### **Menstrual Cycle**

Fluctuation of hormone levels throughout the menstrual cycle has been postulated as an explanation for women's increased vulnerability to rapid cycling. The evidence, however, does not support a neat correspondence between affective state and cycle stage.<sup>174</sup> Nevertheless, mood changes are common throughout the menstrual cycle, though with variable severity, timing, and type of changes.<sup>175</sup>

### **Pregnancy**

During pregnancy, it is critical to maintain euthymia because relapse strongly predicts a difficult postpartum course, including psychosis.<sup>175</sup> For this reason, it is potentially risky to discontinue successful treatments during pregnancy. Unfortunately, continuing treatment is also risky, as several mood stabilizers are associated with risk for teratogenicity. The risks and benefits of each drug must be discussed, as well as the limitations of our knowledge base.

Lithium, which was once considered teratogenic, has been found in recent studies to be safer than expected.<sup>176</sup> Decreasing the lithium dose at onset of labor may help prevent the rapid reduction in vascular volume at delivery, but continuous monitoring of symptoms and lithium serum levels is required to avoid relapse or toxicity during delivery and the immediate postpartum period. Adequate hydration should be maintained, and use of intravenous fluids should be considered for patients undergoing prolonged labor. Valproate and carbamazepine, especially used in combination, have been associated with more serious teratogenic risks than lithium. Lamotrigine appears to be associated with a lower rate of malformations, and it has become a first-line treatment for women of reproductive age with epilepsy.

AAPs are not associated with known teratogenic adverse events, but their association with weight gain, insulin resistance, and diabetes (eg, association of olanzapine with gestational diabetes and preeclampsia) makes use of these medications during pregnancy risky.<sup>176</sup> Thus, weight gain, fasting glucose levels, and blood pressure should be monitored carefully.

Treatment during pregnancy can be managed optimally if the clinician and patient discuss the issue in advance, regardless of reproductive plans.<sup>176</sup> Some women with mild to moderate illness or with a long history of euthymia during prepregnancy treatment may be able to suspend therapy in the first months of pregnancy. However, a mood stabilizer should be introduced either later in pregnancy or in the immediate postpartum period. Breast-feeding concerns should also be discussed.<sup>175</sup>

### Hormonal Contraceptives

As many of the agents (eg, lamotrigine) used to treat bipolar disorder are metabolized by the same hepatic cytochrome P450 enzymes that metabolize hormonal contraceptives, the efficacy of these treatments may be reduced in women using hormonal contraceptives.<sup>177</sup> In turn, other anticonvulsant mood stabilizers (eg, carbamazepine, oxcarbazepine, topiramate) may induce hepatic enzymes that metabolize hormonal contraceptives, reducing their effectiveness. Patients should be informed of this potential interaction and be warned to use additional protective measures, such as condoms.

### Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) affects approximately 2% to 7% of women of reproductive age and involves hormonal as well as metabolic disturbances.<sup>178</sup> PCOS is characterized by elevated androgens (testosterone, androstenedione) and the precursors dehydroepiandrosterone and dehydroepiandrosterone sulfate. Tonic elevations in luteinizing hormone, low normal plasma follicle-stimulating hormone levels, hyperandrogenism, and hyperinsulinemia are common. Insulin resistance plays a role in PCOS pathophysiology: elevated insulin concentrations appear to initiate and promote a cascade of events leading to dyslipidemia, hypertension, and insulin resistance, and to an abnormal reproductive endocrine environment.<sup>178</sup> PCOS symptoms include hirsutism, male pattern alopecia, acne, and menstrual disturbances.

Untreated bipolar women have a higher than average incidence of menstrual dysfunction.<sup>179,180</sup> Some of these women may have undiagnosed comorbid PCOS. However, some medications (eg, valproate) appear to be associated with increased risk for PCOS.<sup>178,180,181</sup> Patients with PCOS risk factors (eg, obesity, blood glucose imbalances)

or with documented PCOS should be referred to specialists (eg, endocrinologists, gynecologists) for further treatment.

### Postpartum Psychosis and Lactation

Women adjusting to the demands of a new infant find the postpartum period highly stressful, and they are at particularly high risk for affective episodes.<sup>182</sup> Women with preexisting psychiatric illness are especially at risk. There is a strong link between postpartum psychosis and bipolar disorder.<sup>183</sup> Given this risk level, psychotropic medications should be continued. Yet, many women wish to breast-feed—raising the question of potential harm to the infant. Data on the safety of using psychotropic medications during breast-feeding are scarce, and most involve women with epilepsy.<sup>182</sup> A good working rule is that the ratio of infant dose exposure to maternal dose should be 10% or less. A formula to use in calculating the amount of drug transferred to the infant is: dose/24 h = concentration of medication in milk × weight (kg) of infant × milk volume /kg ingested in 24 h.

Psychosocial support during this period is essential.<sup>184</sup> A careful, individualized discharge plan must be developed before the patient leaves the hospital. Practical interventions (eg, involving others in the care of the baby so the mother can get adequate sleep), emotional support, and psychotherapy are critical components of this plan.

### Menopause

Like other hormone-mediated reproductive events, menopause is a time of increased vulnerability to relapse or even new-onset bipolar disorder.<sup>185</sup> Almost 30% of women affected by mental illness perceive menopause as worsening psychiatric symptoms.<sup>186</sup> Women who do not undergo hormone replacement therapy during perimenopause and menopause are especially vulnerable.<sup>187</sup> The risks associated with hormone replacement must be weighed against the risk for a psychiatric event.

## NONPHARMACOLOGIC APPROACHES TO MAINTENANCE

Although pharmacotherapy is central to the treatment of bipolar disorder, recent research suggests that combining psychological interventions with medication treatment increases overall effectiveness by further protecting against relapse or recurrence.<sup>188</sup> While the specifics are different, these approaches are complementary. The goals of psychiatric management during maintenance are to establish and maintain the therapeutic alliance, monitor psychiatric status, educate patients regarding bipolar disorder, improve treatment adherence, anticipate stressors, identify new episodes early, and minimize functional impairments.<sup>26</sup>

### Creating a Therapeutic Alliance

For patients with bipolar disorder, there is a correspondence between the patient–clinician therapeutic alliance and their expectations for improvement.<sup>189</sup> The relationship between patient and clinician lies at the heart of the treatment process. An effective therapeutic alliance is based on empathy, trust, authority (not authoritarianism), and ethical considerations such as values, confidentiality,<sup>190</sup> and respect for patient's competence.<sup>191</sup>

## Role of Psychosocial Interventions

Psychosocial interventions include addressing how to endure the neuropsychological disturbances (eg, cognitive impairments) that sometimes accompany severe bipolar illness, and addressing comorbidities, social dysfunction, and nonadherence to treatment.<sup>188</sup> Papadimitriou et al found psychotherapies and psychoeducation potentially useful in the treatment of rapid-cycling bipolar disorder that is resistant to pharmacologic treatment.<sup>192</sup>

## Psychoeducation

According to the literature, psychoeducation improves knowledge of bipolar disorder and treatment options and decreases risk for relapse.<sup>193</sup> Clinicians should remain cognizant that, over time, a patient's ability to understand and retain information—and thus understand the need for long-term treatment—may change. Therefore, education should be ongoing. Print and Internet materials can be helpful with both the patient and the family and significant others (Table 9). Besides simply delivering information, psychoeducation provides bipolar patients with the theory and practice necessary to understand and cope with the consequences of their illness.<sup>188</sup> Colom et al<sup>194</sup> found that mean serum lithium levels were significantly higher and more stable in patients who had received psychoeducation than in patients who had not, even in patients already adhering to their medication regimen. They suggested that psychoeducation does more than enhance adherence; it may well support lifestyle regularity, healthy habits, and early detection of prodromal signs followed by prompt medication intervention.<sup>195</sup>

**Table 9.**  
**Sources of Reliable Educational Materials for Patients**

Source	Web Site
American Psychiatric Association (APA)	www.psych.org
National Alliance on Mental Illness (NAMI)	www.nami.org
National Institute of Mental Health (NIMH)	www.nimh.nih.gov
Bipolar World	www.bipolarworld.net

*Educating patients about lifestyle issues.* Lifestyle changes are an important area for education. Efforts should include educating patients (especially those using AAPs and valproate) about the risk for obesity and about nutrition and exercise approaches to reduce that risk. A nutritionist, a dietician, an exercise therapist, or a group can provide practical assistance as well as emotional support. Smokers and substance abusers also require education and support in their attempts to end their addictions. Group programs may be helpful.<sup>196</sup>

## Therapeutic Modalities

Several therapeutic approaches have shown promise or efficacy in the treatment of bipolar disorder.

*Cognitive behavior therapy.* Research findings regarding the efficacy of this therapy in treating bipolar disorder have been mixed. In a randomized, controlled trial of 253 patients, Scott et al found a significant difference in efficacy between patients who had fewer than

12 episodes and patients who had more than 12 episodes.<sup>197</sup> Lam et al found that the therapy reduced incidence of relapse over the first 12 months of treatment but not thereafter.<sup>198,199</sup> Nevertheless, patients continued to exhibit significantly better mood ratings, social functioning, and coping with bipolar prodromes.

*Interpersonal social rhythm therapy.* This effective therapy for bipolar patients emphasizes maintaining a regular schedule of daily activities and stability in personal relationships.<sup>200</sup> It is based on the idea that disruptions in daily routines and problems in interpersonal relationships can cause mania or depression to recur. After identifying situations that can trigger mania or depression, therapists teach patients how to better manage stressful events and maintain positive relationships. This approach was found effective during acute treatment and succeeded in reducing the likelihood of recurrence during the subsequent 2-year maintenance phase.

*Supportive and psychodynamic therapies.* These therapies are recommended by the APA.<sup>26</sup> Group therapy may help patient and family address issues such as adherence, adaptation to a chronic illness, stigma, self-esteem, and management of other comorbid conditions.

## Working With the Family

Bipolar disorder affects the entire family, not only the patient. On a survey, caregivers for 86 euthymic bipolar patients reported experiencing subjective burden.<sup>201</sup> Caregivers' highest levels of distress concerned the patient's behavior (hyperactivity, irritability, sadness, withdrawal) and the patient's roles in work, study, and social arenas. Caregivers were especially distressed that the patient's illness had affected their own emotional health and life in general. When families are stressed, they are less able to be present for the patient; patients who perceive their close relationships as more remote and of poor quality, with high levels of expressed emotion and marital and family discord, are more likely to experience a recurrence.<sup>202,203</sup> A checklist may help families cope with the disease (Table 10).

Family-focused therapy, a widely investigated family intervention, is designed to improve family functioning by using a combination of communication, problem-solving, and coping strategies; training; psychoeducation; and a relapse prevention study.<sup>204</sup> Combining family therapy and individual therapy with medication treatment may protect episodic bipolar patients from early relapse.

**Table 10. Advice for Families**

- Alert clinician if patient is experiencing prodromal signs of hypomania or depression
- Do not take patient's disturbed behavior personally—see it as a symptom of illness
- Develop action plan to help patient get through each day
- Help patient make and implement sound decisions about employment, school, and relationships
- Nurture yourself as well as the patient; make sure there is a support system in place for all family members, including (if relevant) parents, children, siblings, and spouses
- Ensure adequate supervision of children or dependents, if relevant
- Create plan or contract with patient to ensure safety in event of recurrence

Adapted from Mitchell PB, Ball JR, Best JA, et al. *Med J Aust.* 2006;184:566-570.

## Multidisciplinary Approach

Bipolar patients often struggle with medical and psychiatric comorbidities, as well as with social and family challenges.<sup>188</sup> The effects of an acute episode may include a changed self-image. Treatment must consist of a “package of care”: medical treatment, family and caregiver involvement, and a multidisciplinary approach, possibly involving social services such as adjunct health care (eg, provided by nutritionists) and psychoeducation.

## Maximizing Adherence

Ambivalence about treatment often results in poor adherence to medication regimens and other treatments.<sup>26</sup> Patients may be ambivalent because they lack insight regarding their illness. They may be reluctant to “relinquish their mania.” They may find the practical and financial aspects of long-term treatment burdensome, or they may be unhappy about medication side effects. A review of 39 reports from several medical and psychiatric databases found that negative attitudes toward medication, previous nonadherence, substance abuse, inadequate discharge planning or aftercare environment, and poorer therapeutic alliance were associated with poorer adherence in schizophrenic patients.<sup>205</sup> The same factors might apply to bipolar patients. Adherence is multidimensional: it involves not only patient characteristics, but also factors related to patient–clinician interactions.<sup>54</sup> Adherence is maximized by education, social and professional support, and assistance in removing financial and practical impediments to treatments.

## Preventing Relapse

The possibility of relapse concerns most patients and families. Keeping a mood diary can help patient and clinician track fluctuations in mood long before they rise to the level of prodrome.<sup>206</sup> To remain acutely aware of the signs of prodrome, patient and family can create a “relapse profile”<sup>207</sup> and, when necessary, seek help immediately. Teaching patients to recognize early symptoms of manic relapse and to seek early treatment is associated with important clinical improvements in time to first manic relapse, social functioning, and employment.<sup>208</sup> Patient and family should also have a plan of action in case the prodrome begins. This plan might include having a written contract. (A sample contract may be found at [www.Bipolarworld.net/Family&SOS/contract.htm](http://www.Bipolarworld.net/Family&SOS/contract.htm).)

In the case of incipient prodrome, the clinician must decide whether to hospitalize the patient. Hospitalization should be considered for patients who pose a serious threat of harm to themselves or others, are severely ill and lack adequate social support, demonstrate significantly impaired judgment, have complicating psychiatric or general medical conditions, or have not responded adequately to outpatient treatment.<sup>26</sup> Medication or dose will need to be adjusted; for example, a benzodiazepine may need to be added, or the dose of antipsychotic increased.<sup>207</sup> Suicide risk should be assessed (see next section). The patient should be encouraged to engage in behaviors that may slow progression of the mania—such as establishing a regular routine for eating and sleeping, and intensifying psychological therapies.<sup>207</sup>

## Preventing Suicide

Suicide rates in people with bipolar disorder are generally estimated to be 10% to 19%—15 times that of the general population.<sup>209</sup> However, a

major epidemiologic analysis showed lifetime suicide rates of 29.2% for bipolar patients versus 15.9% for unipolar patients and 4.2% for people with other *DSM-III*–defined Axis I disorders.<sup>210</sup> Suicidal acts, which often come early in the illness course, are associated with severe depressive and dysphoric-agitated mixed phases of illness, especially after repeated severe episodes of depression.<sup>211</sup> Risk factors include family history of suicide, early onset of bipolar disorder, and abuse of alcohol or drugs.<sup>212</sup> Short-term interventions to manage acute suicidality include close clinical supervision, rapid hospitalization, and, if necessary, use of electroconvulsive treatment. Among all interventions used for bipolar disorder, only lithium prophylaxis is associated with consistent major sustained relative reductions in risk for suicides and suicide attempts (approximately 80%).<sup>44</sup>

In suicide prevention, it is important to ask patients if they are contemplating suicide.<sup>146</sup> It is an incorrect assumption that asking about suicide places the idea in the patient’s mind. Rather, patients are often grateful for the opportunity to discuss their fears about suicide.

## TREATING MS B

We return to Ms B, the social work student who presented to the emergency department in a psychotic state. She may begin a 2-medication treatment consisting of lithium or valproate and an AAP (quetiapine, risperidone, or ziprasidone). Olanzapine may be less desirable for Ms B because she is already overweight. Given her fasting glucose of 125 mg/dL, her hirsutism, and her amenorrhea, Ms B may have PCOS, and valproate would not be a first choice. She should begin treatment with lithium and an AAP. In light of her already problematic metabolic profile, her family history of diabetes and hypertension, and the tendency of AAPs to cause weight gain and glucose dysregulation, Ms B should be referred to an endocrinologist for further management.

A hospital social worker helps Ms B and her parents to formulate a discharge plan. Ms B will temporarily withdraw from social work school until her episode has fully resolved and she has been stabilized. She will move in with her parents. The social worker has referred them to an outpatient day program for patients with bipolar disorder, and to a family support group. Ms B is instructed to return in 2 weeks. She is also advised to have further testing for sexually transmitted diseases, as she may have contracted one or more from the strangers with whom she consorted.

After Ms B’s psychosis has resolved, the clinician begins to lower her antipsychotic medication. He also initiates use of lamotrigine to treat Ms B’s emerging depression. Eventually, Ms B is stabilized on a low dose of an antipsychotic, lithium, and lamotrigine. She returns to school and shifts her focus from homelessness to psychiatric patients.

## CONCLUSIONS

Bipolar disorder is a spectrum disorder that can range from mild to severe. Psychosis, whether manic or depressive, can unleash the potential savagery of the condition, with much risk to patient and family. By correctly diagnosing the psychosis and selecting appropriate pharmacologic and nonpharmacologic therapies, the clinician can bring stability to patients, possibly for the first time in their lives. Further research is needed to understand not only the neurobiology and genetics of the disorder, but also the myriad treatments under investigation, new indications for existing medications, and the most effective psychosocial interventions.

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## CME ACTIVITY POSTTEST

Please select only one answer for each question. Circle the letter corresponding to the correct answer on the answer form on the next page. To receive your statement of credit immediately, complete this test online by visiting [www.veritasime.com](http://www.veritasime.com) and entering Activity Login Code BPM.

- Which of the following statements concerning comparisons between bipolar disorder and schizoaffective disorder is true?
  - A misdiagnosis of schizoaffective disorder in a patient with bipolar disorder will not result in medication errors or an accelerated cycling rate, as these conditions have identical pharmacotherapy.
  - Bipolar disorder is a primary mood disorder with psychotic features, while schizoaffective disorder is a primary psychotic disorder with mood features.
  - Schizoaffective disorder and bipolar disorder are both primary psychotic disorders with mood features.
  - A misdiagnosis of bipolar disorder in a patient with schizoaffective disorder will likely result in inadequate mood-stabilizing medications and increase the rate of cycling.
  - The overlap in phenomenology indicates that there is no academic method or practical reason to distinguish these conditions.
- A patient with cycling moods and periods of mood-incongruent psychotic symptoms likely has
  - a primary mood disorder with psychotic features
  - a primary psychotic disorder with periodic mood symptoms
  - unipolar depression
  - posttraumatic stress disorder (PTSD)
  - either a or b
- Patients taking lithium should be monitored regularly for \_\_\_\_\_.
  - hyperprolactinemia
  - metabolic acidosis
  - thyroid abnormalities
  - Stevens-Johnson syndrome
  - all of the above
- The atypical antipsychotics with the most evidentiary support for efficacy and safety in the treatment of acute mania, used adjunctively with a mood stabilizer, are \_\_\_\_\_.
  - quetiapine and ziprasidone
  - olanzapine and aripiprazole
  - quetiapine and risperidone
  - risperidone and olanzapine
  - aripiprazole and ziprasidone
- Female bipolar patients presenting with obesity, hirsutism, male pattern alopecia, acne, and menstrual disturbances may have comorbid \_\_\_\_\_.
  - Stevens-Johnson syndrome
  - metabolic acidosis
  - polycystic ovary syndrome (PCOS)
  - extrapyramidal symptoms (EPS)
  - all of the above
- Which of the following monitoring parameters is/are important for patients taking atypical antipsychotics?
  - weight
  - blood pressure
  - fasting plasma glucose
  - fasting lipid profile
  - all of the above
- Anticonvulsant mood stabilizers sometimes reduce the efficacy of \_\_\_\_\_.
  - antihypertensives
  - antipsychotics
  - hormonal contraceptives
  - benzodiazepines
  - lithium
- Interpersonal social rhythm therapy focuses primarily on \_\_\_\_\_.
  - medication adherence
  - regularity of schedule and stability in personal relationships
  - nutrition and exercise
  - smoking cessation
  - none of the above
- Which intervention improves family functioning by using communication, problem-solving, coping strategies, training, and psychoeducation?
  - psychodynamic therapy
  - interpersonal social rhythm therapy
  - family-focused therapy
  - supportive group therapy
  - none of the above
- What is the recommended way to switch from one antipsychotic to another?
  - discontinue the first agent, wait 1 week, then begin the second agent
  - discontinue the first agent and immediately begin the second agent
  - maintain the dosage of the first agent while adding the second agent
  - titrate the first agent down while titrating the second agent up
  - do not switch agents

# Management of Bipolar Psychosis: Diagnosis and Treatment Strategies

Re-release date: October 2008 • Termination date: March 31, 2010

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	Strongly Disagree	Disagree	Somewhat Disagree	Somewhat Agree	Agree	Strongly Agree
1. The content of this activity is of significant educational value.	1	2	3	4	5	6
2. a. This activity is of significant value to my patient management strategies.	1	2	3	4	5	6
b. If Disagree, please state the reason:						
3. The learning objectives of the activity were achieved.	1	2	3	4	5	6
a. You will be able to accurately diagnose bipolar disorder within the clinical setting, based on criteria delineated in current expert guidelines.	1	2	3	4	5	6
b. Using the guideline recommendations, you will be able to select effective pharmacologic agents to interrupt the psychosis and to create a long-term treatment plan that maintains stability in patients and minimizes chances of recurrence, suicide, and medication adverse effects.	1	2	3	4	5	6
c. You will be able to integrate evidence-based nonpharmacologic approaches into a comprehensive treatment plan.	1	2	3	4	5	6
d. You will be able to identify and manage comorbidities (including substance use disorder and attention-deficit/hyperactivity disorder) and women's disorders (eg, postpartum psychosis, premenstrual syndrome, polycystic ovary syndrome).	1	2	3	4	5	6
4. a. Based on this activity, I intend to make changes to my clinical practice.	-	2	-	-	5	-
b. If Agree, how committed are you to making these changes to your practice? (4=Somewhat Committed, 5=Committed, 6=Strongly Committed)	-	-	-	4	5	6
c. If Agree, please list any changes you plan to make:						
d. If Disagree, please state the reason:						
5. a. The content of this activity is of significant relevance to my practice.	1	2	3	4	5	6
b. If Disagree, please state the reason:						
6. a. I would rate this activity as excellent.	1	2	3	4	5	6
b. If Disagree, please state the reason:						
7. I would rate the method of presentation (monograph) as excellent.	1	2	3	4	5	6
8. I would rate the delivery format (Internet-based) as excellent.	1	2	3	4	5	6
9. a. Do you believe this activity was fair, balanced, and free of commercial bias?	-	2	-	-	5	-
b. If Disagree, please state the reason:						
10. Please list any other topics that interest you, and state your preferred learning format for future educational activities.						
11. A 35-year-old Hispanic woman presents, sobbing and unkempt, with complaints of fatigue, hopelessness, and sadness, which began 7 weeks ago. This patient will receive an antidepressant.	1	2	3	4	5	6
12. A 29-year-old black man presents with agitations and rapid speech, claiming to be the "greatest rap singer of the century." Four weeks earlier, he quit his day job and began working around the clock composing and sending music to the White House. This patient will be diagnosed with schizophrenia or schizoaffective disorder.	1	2	3	4	5	6
13. When determining a treatment plan for patients with bipolar disorder, I will regularly consult expert guidelines, such as TIMA or APA guidelines.	1	2	3	4	5	6
14. In long-term maintenance of patients with bipolar disorder treated with atypical antipsychotics, I will regularly assess for weight gain, dyslipidemia, and elevated blood glucose.	1	2	3	4	5	6
15. I will refer all patients with bipolar disorder for psychosocial interventions.	1	2	3	4	5	6

**Posttest Answer Form**  
(Circle the correct answer to each question)

1. a b c d e    2. a b c d e    3. a b c d e    4. a b c d e    5. a b c d e    6. a b c d e    7. a b c d e    8. a b c d e    9. a b c d e    10. a b c d e

**Request for Credit Form**

Name (please print) \_\_\_\_\_

Degree (check all that apply)  MD/DO  PharmD/RPh  PhD  NP (Lic # \_\_\_\_\_)  RN/LPN/LVN  PA/PA-C  Other (specify) \_\_\_\_\_  None

Clinical specialty(ies)  Endocrinology  Urology  OB/GYN  Cardiology  Internal Medicine  Oncology  Psychiatry  Rheumatology  Primary Care  Pulmonology  Other (specify) \_\_\_\_\_

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I certify that I have participated in this CME activity for a total of \_\_\_\_\_ **AMA PRA Category 1 Credits™**.

Signature \_\_\_\_\_ Date \_\_\_\_\_