

**THE PRIMARY CARE COMPANION**  
**TO THE JOURNAL OF CLINICAL PSYCHIATRY**  
**CME ACTIVITY**

VOLUME 9 NUMBER 5

CME ARTICLE

**Academic Highlights: Managing Bipolar Disorder  
From Urgent Situations to Maintenance Therapy**



# Managing Bipolar Disorder From Urgent Situations to Maintenance Therapy

**T**his ACADEMIC HIGHLIGHTS section of The Primary Care Companion to The Journal of Clinical Psychiatry presents the highlights of the planning teleconference series "Managing Bipolar Disorder From Urgent Situations to Maintenance Therapy," which was held in March and April 2007. This report was prepared by the CME Institute of Physicians Postgraduate Press, Inc., and was supported by an educational grant from Eli Lilly and Company.

The teleconferences were chaired by **Rakesh Jain, M.D., M.P.H.**, from R/D Clinical Research, Inc., Lake Jackson, Tex. The faculty were **J. Sloan Manning, M.D.**, from the Mood Disorders Clinic, Moses Cone Family Practice Residency, and private practice, Greensboro, N.C.; **Steven J. Garlow, M.D., Ph.D.**, from the Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Ga.; **Tracey G. Skale, M.D.**, from Greater Cincinnati Behavioral Health Services, Cincinnati, Ohio; **W. Clay Jackson, M.D., Dip.Th.**, from the Department of Psychiatry, University of Tennessee, Memphis; **Noel C. Gardner, M.D.**, from the Department of Psychiatry, University of Utah School of Medicine, Salt Lake City; and **Vladimir Maletic, M.D.**, from the Department of Neuropsychiatry and Behavioral Science, University of South Carolina School of Medicine, Columbia.

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## Introduction: Urgent and Maintenance Management of Bipolar Disorder

*Urgent* is defined as "calling for immediate attention."<sup>1</sup> Rakesh Jain, M.D., M.P.H., began the discussion by noting that patients with bipolar disorder often need immediate care from clinicians, because these patients are at high risk for urgent situations, such as suicidality, aggression, legal difficulties, functional disability, occupational disruption, and marital disharmony. Suicidality is one of the most urgent situations that can occur for patients with bipolar disorder; overall, they have a higher risk of suicide than the general population (standardized mortality ratio = 9.77, 95% CI = 4.22 to 19.24).<sup>2</sup> Clinicians have long been aware of the common occurrence of aggression and agitation in unstable patients with bipolar disorder.<sup>3</sup> The National Comorbidity Survey (NCS)<sup>4</sup> and the Epidemiologic Catchment Area Survey<sup>5</sup> found high rates of violence among patients with bipolar disorder (16% and 11%, respectively). Uncontrolled bipolar disorder increases an individual's risk for criminal arrest, thereby creating clinical urgency for rapid intervention so that patients may avoid incarceration.<sup>6</sup>

Bipolar disorder is also associated with severe impairment of social, vocational, and cognitive functioning.<sup>7</sup> Dr. Jain noted that relationships and marriages are adversely affected when a partner suffers from bipolar disorder. For example, evidence<sup>8</sup> has shown high rates of sexual dissatisfaction and low rates of affection, support, and consideration for spouses of patients with bipolar disorder, all of which results in high rates of marital discord in this population. In terms of

vocation, according to the NCS Replication,<sup>9</sup> patients with bipolar disorder lost 65.5 workdays per year. When compared with patients with major depressive disorder, who lost 27.2 workdays per year, bipolar disorder emerges as one of the most disabling psychiatric conditions.

Clinicians, including those in the primary care setting, have an important role in the quick and efficient identification and resolution of urgent situations for patients with bipolar disorder, although some may not feel confident on how to best diffuse urgent situations and guide patients to stability. Dr. Jain suggested that clinicians first identify whether the patient is presenting with a manic, depressive, or mixed episode when treating a patient with bipolar disorder. The symptoms should be treated to full resolution and the patient should be transitioned to an effective maintenance treatment. However, these steps are not always easily executed. For example, accurate identification of bipolar disorder is still suboptimal in both psychiatric and nonpsychiatric settings. Dr. Jain referred to a survey<sup>10</sup> that found that 69% of patients with bipolar disorder were initially misdiagnosed. Another study<sup>11</sup> of adult patients with depression who were screened for bipolar disorder at a primary care clinic found that nearly two thirds of patients who screened positive had never received a diagnosis of bipolar disorder.

Dr. Jain explained that complete cessation of manic, depressive, or mixed symptoms should be the ultimate goal of bipolar disorder treatment, but residual symptoms can still

be far too common. The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD)<sup>12</sup> found that not only do many patients have residual symptoms, but these symptoms are associated with high rates of relapse. Dr. Jain noted that Emil Kraepelin<sup>13</sup> described bipolar disorder almost a century ago as having a prolonged course, with relapse being the rule rather than the exception. Relapse remains a critical problem for patients

with bipolar disorder and clinicians who treat the illness. The importance of maintenance therapy to help patients stay in remission is widely recognized by clinicians.

Effective pharmacologic and non-pharmacologic treatments are available to help manage patients in urgent situations and in maintenance therapy. Dr. Jain emphasized that clinicians should implement these interventions to improve both short- and long-term pa-

tient outcomes, keeping in mind that problems can arise due to medication noncompliance<sup>14</sup> or unnecessary or ineffective treatments.<sup>15</sup> Dr. Jain then introduced expert clinicians in the field of bipolar disorder who described how to take control of patients in urgent situations and provide evidence-based recommendations and clinical advice on how to effectively manage the maintenance phase of bipolar disorder treatment.

## Importance of a Correct Initial Diagnosis for Bipolar Mixed Episodes

Correct initial diagnosis and stabilization of acute bipolar episodes is necessary to avoid social and economic consequences. J. Sloan Manning, M.D., explained that because the phenomenology of bipolar illness is varied, in that manic and depressive symptoms often manifest concurrently and are often comorbid with other features of psychopathology, these symptoms can be easily confused with symptoms of other psychiatric illnesses or missed altogether during the clinical process. An assessment for bipolar mixed episode or mixed states is an important part of the clinical evaluation of any depressed and anxious patient. If an early and accurate diagnosis is not made, the patient may not receive focused and effective treatment. In fact, some prescribed medications may exacerbate the current mixed episode or state.

### Concepts of Mixed States

The key concept for understanding bipolar mixed states, according to Dr. Manning, is that mood, cognition, and psychomotor energy can change independently of one another. For example, the extremes of a pure mood state, either mania or depression, can be superimposed onto cognitive or psychomotor features of the opposite mood state.<sup>16</sup> Therefore, bipolar disorder can present with symptoms of both mania and depression simultaneously, creating a myriad of symptoms that can be confusing to clinicians.

The *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR)<sup>17</sup> criteria for a mixed episode require at least 1 week during which the criteria for both a manic episode and a major depressive episode are met almost daily. DSM-IV-TR characteristics of mixed episodes include rapidly fluctuating moods, agitated states, severe insomnia, psychotic features, and increased suicidality. Dr. Manning stated that the DSM-IV-TR concept of bipolar disorder mixed states is categorical and limited. It excludes episodes that might be direct physiologic effects of general medical conditions, such as neurologic disorders, as well as the effects of substances, such as amphetamines, neurotoxins, and antidepressants.

Non-DSM-IV-TR concepts of mixed states include dimensional mixing and trait mixing. Dr. Manning observed that definitions of dimensional mixing vary, but may involve dysphoric mania, which is a manic state combined with 2 or more depressive symptoms,<sup>18</sup> or a depressive mixed state, which is major depression combined with 3 or more hypomanic symptoms.<sup>19</sup> In the concept of trait mixing,<sup>20</sup> the syndromal depression or mania presents with features of the opposite temperament. For example, patients who have primarily depressive temperaments carry those depressive traits into manic episodes. Conversely, patients with early-onset, habitual, low-grade

manic symptoms carry those manic traits into major depressive episodes.

### Evaluating Patients With Mixed States

Dr. Manning stated that suicidality is perhaps the most serious reason why accurate initial diagnosis of bipolar mixed states is critical in clinical practice. Research<sup>21,22</sup> has shown that both fatal and nonfatal suicidal behaviors are increased during mixed episodes compared with pure manic episodes (55% vs. 2%, respectively). Therefore, patients in mixed states are quite ill, and clinicians should be mindful of potential mortality risks when evaluating them. During patient evaluations, it is also helpful for clinicians to consider social and financial problems as possible indicators of a mood disorder. Mixed states often lead to marital disruptions,<sup>10</sup> employment disruptions,<sup>23</sup> involvement with the legal system,<sup>23</sup> and high utilization of medical resources.<sup>24</sup>

Dr. Manning explained that the concept of mixed states is unfamiliar to many clinicians, which creates opportunities for the misdiagnosis and the mistreatment of patients. Studies<sup>11,25</sup> have found that about one fourth of patients who presented with symptoms of depression or anxiety in primary care had some form of bipolar disorder. Because anxiety disorders and suicidal behaviors occur frequently in bipolar patients, clinicians tend to

**Table 1. Features of Mixed States**

Unrelenting dysphoria <sup>a</sup>
Severe agitation <sup>a</sup>
Refractory anxiety <sup>a</sup>
Unendurable sexual excitement <sup>a</sup>
Intractable insomnia <sup>a</sup>
Suicidal obsession and impulses
Histrionic demeanor
Genuine, intense suffering
<sup>a</sup> Based on Akiskal and Mallya. <sup>28</sup>

focus on comorbid anxiety and depression and may miss a diagnosis of bipolar disorder. If depression or anxiety is the clinician's sole focus, then the patient with bipolar disorder may be treated with antidepressants, which can increase the potential for suicidality, impulsivity, and aggressive tendencies.<sup>26</sup> In addition, patients in mixed states often report refractory insomnia and suicidal tendencies, leading clinicians to overmedicate patients with

sedative hypnotics.<sup>27</sup> To prevent misdiagnosis, Akiskal and Mallya<sup>28</sup> created a clinically useful list of features to accurately identify mixed states (Table 1).

### Conclusion

Dr. Manning concluded by stating that many clinicians in primary care may find the notion of mixed states counterintuitive in that some patients with bipolar disorder may not only experience pure manic or pure depressed episodes, but concurrent manic and depressive symptoms and episodes. If mixed episodes or states are not recognized, accurately diagnosed, and effectively treated with the appropriate interventions, clinicians will miss the opportunity to reduce mortality and to improve the overall outcome for patients with bipolar disorder.

is accompanied by psychosis. Immediate intervention at this stage is critical to prevent harm to both patients and their caregivers.

Ideally, an oral agent, as opposed to an injectable formulation, should be administered to relieve agitation. If the clinician can convince the patient to voluntarily ingest an oral agent, conflict is avoided and a therapeutic alliance between the patient and the clinician is established. Dr. Garlow conceded that circumstances do arise wherein a patient will not cooperate, and an intramuscular agent must be used. However, in this situation, the treatment should be aimed at calming rather than sedating the patient; the patient should remain alert enough to participate in his or her own evaluation and treatment.

Several pharmacologic agents are available for the treatment of agitation during an acute manic episode. The conventional antipsychotic haloperidol<sup>30</sup> has long been used for agitation, but Dr. Garlow recommended treating patients with atypical antipsychotics instead, because of their lower risk of sedation. Intramuscular olanzapine<sup>31</sup> and aripiprazole<sup>32</sup> are the only 2 agents indicated by the Food and Drug Administration (FDA) for the treatment of agitation in bipolar mania (Table 2), although intramuscular ziprasidone<sup>33</sup> is often used. Dr. Garlow stated that the benzodiazepine lorazepam is also useful for alleviating agitation when used either as a monotherapy or in combination with an antipsychotic.

For new-onset acute manic episodes that are not marked by agitation, many pharmacologic options are available. Lithium<sup>34</sup> has been the standard medication for manic episodes in bipolar disorder. Effective, FDA-approved treatments for acute mania are the conventional antipsychotic chlorpromazine,<sup>35</sup> divalproex sodium,<sup>36</sup> and extended-release carbamazepine.<sup>37</sup> Oral formulations of risperidone,<sup>38</sup> olanzapine,<sup>31</sup> ziprasidone,<sup>33</sup> quetiapine,<sup>41</sup> and aripiprazole<sup>32</sup> are all indicated for new-onset manic episodes.

## Pharmacologic Interventions for New-Onset and Breakthrough Acute Mood States

Steven J. Garlow, M.D., Ph.D., discussed pharmacotherapy for 3 types of new-onset or breakthrough acute mood episodes: manic, depressive, and mixed. Manic episodes can cause severe behavioral disturbances, activation, psychosis, and agitation; depressive episodes can cause neurovegetative symptoms and psychosis; and mixed episodes can cause agitation, distress, and psychosis. When patients present in an acute bipolar mood episode, they may or may not already be receiving treatment. Untreated patients may not be receiving treatment because they have never been diagnosed and treated or they have stopped taking their maintenance medication. Alternatively, patients may present with a breakthrough episode that occurs despite adhering to maintenance pharmacotherapy.

Dr. Garlow emphasized the overall treatment goals for patients in acute mood episodes: rapid relief of symptoms and transition into maintenance

therapy that will prevent or minimize mood cycling. Rapid relief of acute symptoms is critical because of the high risk of suicide<sup>29</sup> and the devastating consequences that an acute mood episode can have on a patient's life. Urgent intervention in acute mood episodes is necessary to prevent hospitalization or shorten a hospital stay that may be stressful and demoralizing for the patient.

### New-Onset Manic or Mixed Episodes

Agitation may be the first acute manifestation of bipolar mania. Dr. Garlow defined *agitation* as excessive motor activity associated with a feeling of inner tension. Agitated patients may exhibit considerable amounts of mood lability, impulsivity, and motor agitation, the experience of which is highly distressing, tiring, and uncomfortable for patients. Agitation may also cause patients to feel threatened, which can lead to dangerous or aggressive behaviors, especially if agitation

**Table 2. FDA-Approved Agents for the Treatment of Various Bipolar Disorder States**

Agent	Agitation	Type of Mood Episode			Adjunctive Medications
		Manic	Mixed	Depressed	
Aripiprazole <sup>32</sup>	✓ <sup>a</sup>	✓	✓		✓
Carbamazepine <sup>37</sup>		✓ <sup>a</sup>	✓ <sup>a</sup>		
Chlorpromazine <sup>35</sup>		✓			
Divalproex <sup>36</sup>		✓ <sup>a</sup>	✓ <sup>a</sup>		
Lamotrigine <sup>42</sup>					✓
Lithium <sup>34</sup>		✓			✓
Olanzapine <sup>31</sup>	✓ <sup>a</sup>	✓	✓		✓
Olanzapine-fluoxetine <sup>39</sup>				✓	
Quetiapine <sup>41</sup>		✓		✓	
Risperidone <sup>38</sup>		✓	✓		
Ziprasidone <sup>33</sup>		✓	✓		

<sup>a</sup>Indicates extended-release or intramuscular injectable formulations.

Symbol: ✓ = approved by the U.S. Food and Drug Administration (FDA).

A number of atypical antipsychotics and anticonvulsant agents are indicated for the treatment of acute mixed episodes including: risperidone,<sup>38</sup> olanzapine,<sup>31</sup> ziprasidone,<sup>33</sup> aripiprazole,<sup>32</sup> and the extended-release formulations of both carbamazepine<sup>37</sup> and divalproex sodium.<sup>36</sup> (see Table 2).

### New-Onset Depressive Episodes

Dr. Garlow stated that rapid relief of new-onset depressive episodes, which are characterized by negative cognitive symptoms and their associated impairments, may be achieved by a number of pharmacologic interventions. The olanzapine-fluoxetine combination<sup>39</sup> and quetiapine<sup>40,41</sup> as monotherapy are indicated for treating bipolar depression (see Table 2). Lamotrigine, lithium, and divalproex sodium may relieve depressive symptoms effectively, although they are not approved for this use. Lithium and divalproex sodium may each be used alone as monotherapies or, when treating an urgent situation, in combination with an antidepressant<sup>43</sup> for a short time. Although antidepressants can be effective short-term treatments for bipolar depression,<sup>44,45</sup> the use of these agents is controversial owing to concerns that antidepressants may not be particularly efficacious in this condition and may cause patients to cycle into mania or begin rapid cycling.<sup>46,47</sup> Therefore, antidepressants should only be used

in combination with other mood-stabilizing agents, such as lithium, divalproex sodium, or olanzapine. Selective serotonin reuptake inhibitors (SSRIs) are preferable when treating patients with bipolar disorder to tricyclic antidepressants, because SSRIs are less likely to induce mania.<sup>45</sup>

### Breakthrough Episodes

Treatment considerations for breakthrough episodes in patients on maintenance therapy differ from those for new-onset urgent situations. Prior mood polarity may predict the polarity of the next episode.<sup>48</sup> Particular symptoms may also indicate in which direction the patient is cycling. For example, sleep disturbances may indicate a switch into mania, and sadness, anxiety, poor concentration, or indecisiveness may indicate emergent depression. Dr. Garlow recommended that the first step in the treatment of any breakthrough episode should be to optimize the dose of the maintenance agent. If symptoms persist, a second agent may be added.

In the event that a new agent is added to the maintenance treatment during a breakthrough episode, the patient's history and preferences should be the primary considerations when selecting the adjunctive treatment. Atypical antipsychotics are effective adjunctive agents for breakthrough manic, mixed, and depressive

episodes.<sup>49,50</sup> For manic episodes, risperidone,<sup>38</sup> olanzapine,<sup>31</sup> and quetiapine<sup>40</sup> are all indicated for use with the maintenance treatments lithium and divalproex sodium. Risperidone<sup>38</sup> and olanzapine<sup>31</sup> are FDA-approved adjunctive agents for breakthrough mixed episodes. For breakthrough depressive episodes, Dr. Garlow advocated using the following pharmacotherapies for patients already taking a maintenance medication: the olanzapine-fluoxetine combination,<sup>39</sup> quetiapine,<sup>40</sup> a mood stabilizer, such as lamotrigine,<sup>42</sup> or an antidepressant.<sup>50-53</sup>

### Conclusion

Dr. Garlow concluded that immediate intervention during an acute bipolar episode can avert or minimize hospitalization and prevent catastrophic consequences for the patient. Patient characteristics, such as treatment history, cycling patterns, and current mood state, should all be considered during treatment selection. Clinicians should select agents with a rapid and robust onset of action. Ideally, treatment of acute episodes should be designed to provide as smooth a transition into maintenance therapy as possible, because successful maintenance therapy is the long-term treatment goal for patients with bipolar disorder.

### Practical Strategies for Assessing and Stabilizing Patients in Urgent Situations

Tracey G. Skale, M.D., noted that clinicians have a number of sources of information at their disposal concerning treatment options, including scholarly articles, treatment algorithms, and medication package inserts. In light of these sources for treatment recommendations, Dr. Skale posed the question, what actions should a physician take when a patient presents in an acutely manic, mixed, or depressed bipolar state? Dr. Skale went on to detail practical approaches that psychiatric and

nonpsychiatric clinicians can employ to ensure safe and rapid reduction of symptoms for bipolar patients in urgent situations.

### The Biopsychosocial Model

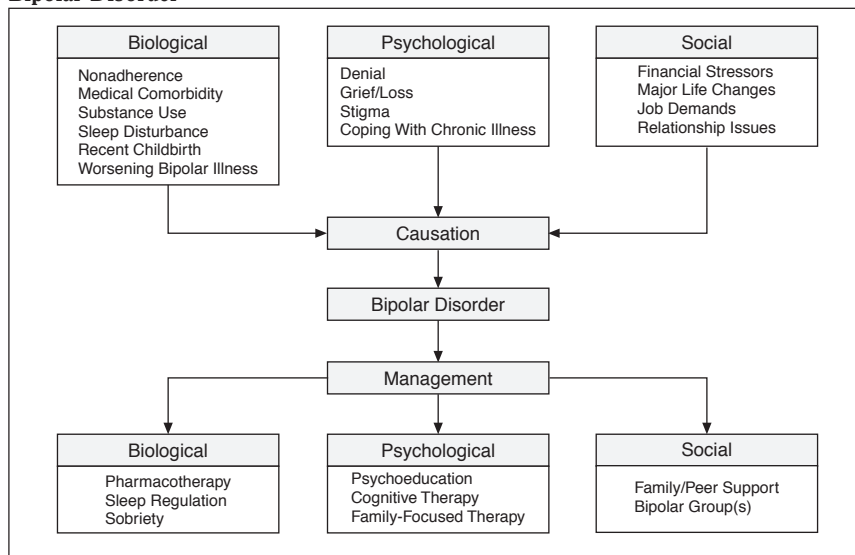
Biological, psychological, and social factors affect the development and the treatment of acute bipolar states. Dr. Skale presented the biopsychosocial model to illustrate patient issues that can precipitate or be symptomatic of a bipolar urgent situation and proposed management strategies to optimally treat the various aspects of bipolar disorder (Figure 1).

For biological factors, pharmacotherapy can reduce the symptoms of an acute bipolar state or episode. Additionally, because substance abuse and insomnia can be both triggers and symptoms of acute states in patients with bipolar disorder,<sup>54,55</sup> tools for sobriety and sleep regulation help patients recover from current acute episodes, avoid future urgent situations, and focus on the underlying psychiatric issue of bipolar disorder.

Dr. Skale went on to explain that psychoeducation is a psychological management tool<sup>56</sup> through which the patient learns about his or her unique symptoms, the recurrent nature of the illness, and the importance of medication adherence. Cognitive therapy<sup>57</sup> and family-focused therapy<sup>58</sup> can also help the patient and the patient's family cope with bipolar disorder as a chronic, lifelong illness.

Socially, the clinician can help the patient connect with family or peer support groups, such as the Depression and Bipolar Support Alliance and the National Alliance on Mental Illness. According to Dr. Skale, voluntary or involuntary hospitalization is typically reserved for patients at imminent risk of harming themselves or others<sup>23</sup>; however, partial hospitalization, referral to a crisis stabilization center, and intensified contact with mental health care professionals<sup>58</sup> are also social management tools for stabilization.

**Figure 1. Biopsychosocial Model for Urgent Situations in Patients With Bipolar Disorder**



When faced with a patient in an urgent situation, Dr. Skale recommended that clinicians routinely ask themselves specific questions that address all 3 areas—biological, psychological, and social—to avoid overlooking an issue that could affect the patient's outcome. These questions include the following<sup>54,55</sup>:

- Is the patient presenting in an acute manic, depressed, or mixed episode?
- Is the patient at risk for committing suicide or homicide?
- Is the patient aggressive?
- Is the patient currently experiencing psychotic symptoms?
- Is there comorbid alcohol or substance use?
- Is the patient pregnant?
- Are there any other medical concerns?
- What medications and supplements is the patient taking?
- Does the patient have adherence problems with any prescribed medication?
- What are the patient's current family, social, and occupational challenges?

### Pharmacotherapy

Acutely manic patients are in need of immediate and aggressive pharmacologic therapy.<sup>54</sup> Dr. Skale identified 3 criteria that clinicians can use to select the most effective pharmacologic intervention(s) for individual patients: (1) the need for the medication to be effective, (2) the need for the medication to work quickly, and (3) the need for the medication to be well tolerated. If the patient has taken a medication that proved to be effective and well-tolerated in the past, then that same medication may be an effective choice to treat the present urgent situation. In the case of a breakthrough episode, the clinician also has the option of optimizing the current dose of maintenance therapy or adding any adjunctive medication. The clinician should also administer routine laboratory testing and a drug screening as soon as possible.<sup>55</sup>

If the patient is currently prescribed an atypical antipsychotic, the clinician should consider increasing the dose to resolve the urgent situation. For example, 2 mg/day of risperidone can be temporarily increased to 4 mg/day, olanzapine can be increased from 15 mg/day to 20 mg/day or higher if needed. The goal of treatment in urgent situations, according to Dr. Skale,

is to avoid suicide attempts, aggression, the potentially devastating consequences of impulsivity, and costly hospitalizations. Once the acute bipolar episode has been resolved, the patient's symptoms can typically be managed at a lower dose of medication. Dr. Skale advised that conventional antipsychotic medications can be used, although these agents are not highly recommended by the American Psychiatric Association (APA)<sup>55</sup> because of the risk of acute dystonic reactions.

According to the APA,<sup>55</sup> benzodiazepines can temporarily be added to an inpatient medication regimen to quickly calm manic symptoms and to soothe anxiety and insomnia. Dr. Skale stressed that benzodiazepines should be avoided in outpatient situations if possible because of the possibility of abuse and dependence. The clinician may also start the patient on mood-stabilizer treatment, optimize the patient's current mood stabilizer dose within the appropriate efficacy and tolerability range, or augment the current mood stabilizer with another mood stabilizer. However, Dr. Skale stated that lithium may not be the most effective intervention for an outpatient in an urgent situation, because lithium has a relatively long onset of action and therefore cannot rapidly relieve acute manic, depressive, or mixed episode symptoms.

### Complicating Factors

Dr. Skale emphasized that suicidality can be present in any state of bipolar disorder. Utilizing both pharmacologic and nonpharmacologic treatment tools is critical when managing a suicidal patient in a manic, depressed, or mixed episode. APA guidelines<sup>55</sup> recommend that the clinician assess suicidal or homicidal ideation, intent, or plan. Also, patient access to the means of suicide and the lethality of those means must be assessed, along with the possible presence of hallucinations and severe anxiety. The clinician should also screen a suicidal patient for the presence of alcohol or

substance use, history of previous suicide attempts, and family history of suicide. The clinician may also inquire if the patient has been recently exposed to a suicide, such as the suicide of a friend or relative.

Another factor that may complicate treatment of an acute mood episode is the presence of psychotic symptoms. Dr. Skale reported that as many as half of patients with bipolar disorder may present with psychotic symptoms during an acute episode.<sup>54,55</sup> In an emergency department, intramuscular formulations of ziprasidone, olanzapine, and aripiprazole may be used to gain control of an aggressive or psychotic patient for safety reasons. An alternative to intramuscular formulations is the orally disintegrating tablet, which is an available formulation for risperidone, olanzapine, and aripiprazole. This type of medication delivery can be helpful in an urgent situation, and alternative delivery methods can also be used to improve patient adherence.

Substance misuse can confound the clinical picture as well, according to Dr. Skale. Patients with bipolar disorder have higher rates of substance misuse than the general population. In fact, 46% of patients with bipolar disorder have been shown to be alcohol dependent, compared with 13% of the

general population, and 41% of patients have been shown to misuse other substances, while only 6% of the general population have been shown to misuse other substances.<sup>59</sup> Alcohol consumption in particular can complicate lithium treatment because dehydration from alcohol consumption can increase lithium levels to toxic levels. Hepatic dysfunction from chronic alcohol consumption or hepatitis from intravenous substance use may adversely affect plasma levels of valproate or carbamazepine.<sup>60</sup>

If the patient is pregnant, the usual pharmacologic interventions may not be appropriate. For example, lithium, valproate, and other anticonvulsants should be avoided during the first trimester.<sup>61,62</sup> In addition, postpartum patients are at high risk for relapse into mania, depression, or psychosis, with a relapse rate as high as 50%.<sup>63</sup>

### Conclusion

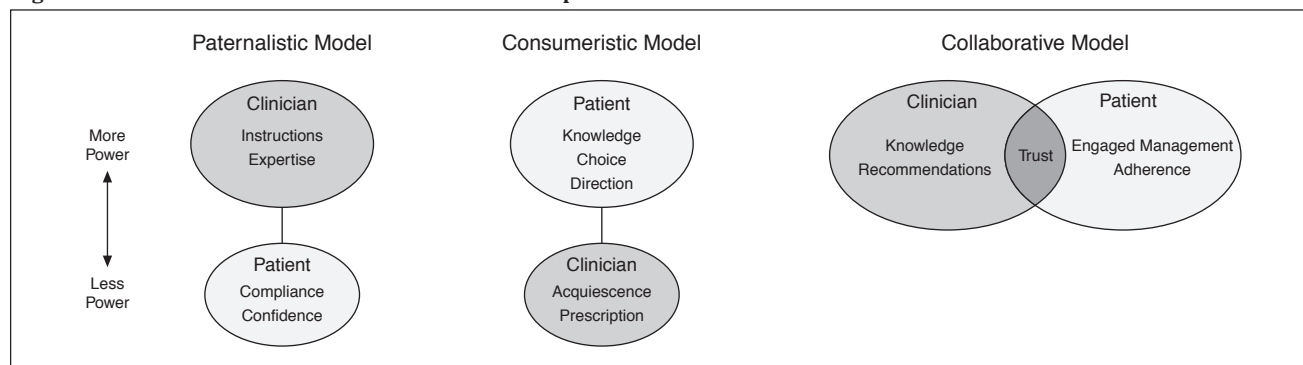
Dr. Skale closed by stating that urgent situations present frequently in clinical settings. Optimizing outcomes for patients with bipolar disorder in crisis situations requires clinicians to rapidly and accurately assess biopsychosocial precipitants and offer the appropriate corresponding interventions.

## Facilitating Adherence in Maintenance Therapy

The goals of therapy differ according to the phase in which the patient presents,<sup>64</sup> noted W. Clay Jackson, M.D. The goal of maintenance therapy is for the patient to remain stable and resume his or her normal functioning after attaining syndromal recovery in the acute phase of treatment. Barriers to maintaining stability include recurrent episodes, which are common during the maintenance phase of therapy,<sup>54</sup> the lag between symptomatic and functional recovery,<sup>65</sup> medical and psychiatric comorbidities,<sup>66,67</sup> and suboptimal quality of care.<sup>68</sup>

### Factors That Affect Treatment Adherence

One of the main barriers to effective treatment of bipolar disorder is patient nonadherence to clinician-recommended therapy. According to a recent study,<sup>69</sup> 45% of patients with bipolar disorder are nonadherent with pharmacotherapy. Nonadherence to mood-stabilizer treatment predicts higher utilization of health care resources, including psychiatric emergency visits and psychiatric hospitalizations.<sup>70</sup> Because proper adherence to treatment can increase the chances

**Figure 2. Models for the Patient-Clinician Relationship**

of symptomatic and functional recovery, lessen the severity and mortality of bipolar disorder, and reduce the economic costs of bipolar disorder, treatment adherence is an important goal for patients and their clinicians during maintenance treatment.

According to Dr. Jackson, a key determinant in maintenance treatment is the therapeutic alliance between the clinician and patient. The choice of treatment itself is a part of this alliance because of the cost, possible adverse effects, and ease of use of different medications. Other variables that affect the therapeutic alliance include the patient's insight into his or her illness, insight into the available treatments, and logistical challenges faced by the patient, such as making and keeping appointments with health care providers and acquiring insurance coverage.

Additionally, patients can be conflicted about taking medication and adhering to treatment.<sup>71</sup> The internal negotiations patients experience when they are conflicted about taking medication are determined by the patient's self-identity. These negotiations are associated with a fear of medication dependency, the belief that the medication is a symbol of the patient's mental illness, and the worry that the medication is being used as an experiment on the patient. External treatment negotiations involve the patient's clinical identity and include concerns about the type, dose, and route of medication.<sup>71</sup> In light of these potential psychological

conflicts, nonadherence may be better framed by the clinician as a developmental phase that can be worked through rather than as a static, categorical response.

#### How the Therapeutic Alliance Influences Adherence

Although improved treatment efficacy, safety, and tolerability of medication can positively impact treatment adherence, patients must also be willing to take medication and participate in their therapy. The relationship between patient and clinician has a substantial effect on the patient's willingness to continue adhering to treatment. Dr. Jackson stated that patients do not believe in the doctor because of the medicine; rather, they believe in the medicine because of the doctor. Clinicians can therefore positively influence adherence by maintaining therapeutic alliances with their patients.<sup>72</sup>

The level of clinician-patient concordance—defined as the degree to which the patient and the clinician view the illness and its treatment in the same way—and the relationship between concordance and adherence affect the clinician's treatment strategy. For a patient who is already both concordant and adherent, the clinician will best facilitate compliance by maintaining concordance through recognizing collaborative therapeutic outcomes and building external support for and with the patient. If a patient is concordant but not adherent, the patient will be-

lieve what the clinician states about the illness but will be unable to adhere to treatment for some other reason. The clinician's role in this scenario, according to Dr. Jackson, is to examine the patient's barriers to adherence and to work to overcome those barriers. If the patient is adherent but discordant, the clinician should work to improve concordance by recognizing the patient's own self-interest and provide options for improved therapeutic outcomes. The clinician should then help the patient take charge of his or her own care. For a patient who is nonadherent and discordant, the clinician should establish a therapeutic alliance by clarifying the areas of agreement between clinician and patient and by explaining to the patient that a lack of collaboration can result in negative outcomes.

#### Past and Present Models of the Therapeutic Alliance

Dr. Jackson reviewed the paternalistic,<sup>73,74</sup> consumeristic,<sup>75</sup> and collaborative<sup>76</sup> models of the therapeutic alliance (Figure 2). In the paternalistic model,<sup>73,74</sup> the clinician had greater power and authority than the patient. The clinician gave instruction to the patient and provided expertise. The patient was expected to have confidence in the clinician and to comply with his or her instructions. The paternalistic model, which gives little voice to the patient, is rarely practiced today.

In the consumeristic model,<sup>75</sup> the patient has greater power and authority

than the clinician. The patient controls the therapeutic alliance, demonstrates knowledge of the disease and treatment, exercises freedom of choice, and has a voice in the direction of his or her therapy. In this model, the clinician is expected to acquiesce, within reason, to therapies requested by the patient. The consumeristic model may not work for patients with bipolar disorder because their ability to direct their own care may be compromised by their illness.

In the collaborative model,<sup>76</sup> the clinician and the patient have overlapping spheres of power and responsibility. The clinician provides knowledge and makes recommendations regarding treatment. The patient is expected to be engaged in his or her own disease management and to be adherent to treatment. The collaborative model is driven by trust. For the collaborative model to work positively in bipolar

disorder, the clinician and patient should have an open dialogue, wherein the clinician provides expert knowledge about treatment and listens to the patient's input and concerns about treatment.

### Conclusion

In conclusion, Dr. Jackson stated that a strong treatment alliance is associated with a decrease of depressive and manic symptoms and complications of bipolar disorder and an increase in the reporting of beneficial and accessible social support by patients.<sup>72</sup> Strong therapeutic alliances help patients have positive attitudes regarding medication and mitigate the perceived stigma of a diagnosis of bipolar disorder. All of these factors help increase adherence to maintenance treatment, thus improving the outcome of treatment and quality of life for patients with bipolar disorder.

patients. The key to implementing treatment guidelines in clinical practice is to take into account individual patient needs when using guidelines. In this way, the clinician practices evidence-based medicine. Currently, 3 prominent U.S. treatment guidelines, the Texas Medication Algorithm Project,<sup>85</sup> the Expert Consensus Guideline Series,<sup>90</sup> and STEP-BD<sup>91</sup> support the importance of maintenance treatment, despite limited data on maintenance treatment options.

Dr. Gardner went on to describe the systematic iterative approach for the treatment of bipolar disorder used in STEP-BD.<sup>91</sup> In this approach, physicians make informed decisions at each step of treatment (called *critical decision points*) based on the combination of individual patient needs and physicians' clinical expertise, including their knowledge of scientific evidence such as information about drug safety, efficacy, and tolerability (Figure 3).<sup>92</sup> At each critical decision point, such as an acute manic or mixed state, clinicians develop a menu of reasonable treatment options.<sup>91</sup> Once the menu is developed, the clinician can educate the patient and work with him or her to find a treatment plan to which the patient can commit. The clinician will monitor and measure the treatment outcomes, weighing the benefits against the problems of treatment. Dr. Gardner asserted that while the STEP-BD<sup>91</sup> model is effective, it is limited to bipolar I acute manic and mixed states, even though it implies that sequential treatment is an ongoing process that should move into the maintenance phase.

## A Clinician's View of the Data on Maintenance Treatment of Bipolar Disorder

Dr. Noel C. Gardner opened by saying that, because bipolar disorder is characterized by chronic relapses and recurrent syndromal and subsyndromal symptoms,<sup>17,77-79</sup> treating bipolar disorder requires more than just stabilization of the acute episode. Effective maintenance can prevent relapse<sup>80,81-83</sup>; reduce subsyndromal symptoms; decrease hospitalizations, morbidity, and mortality<sup>84</sup>; and improve functioning and quality of life.

### Evidence-Based Medicine in the Treatment of Bipolar Disorder

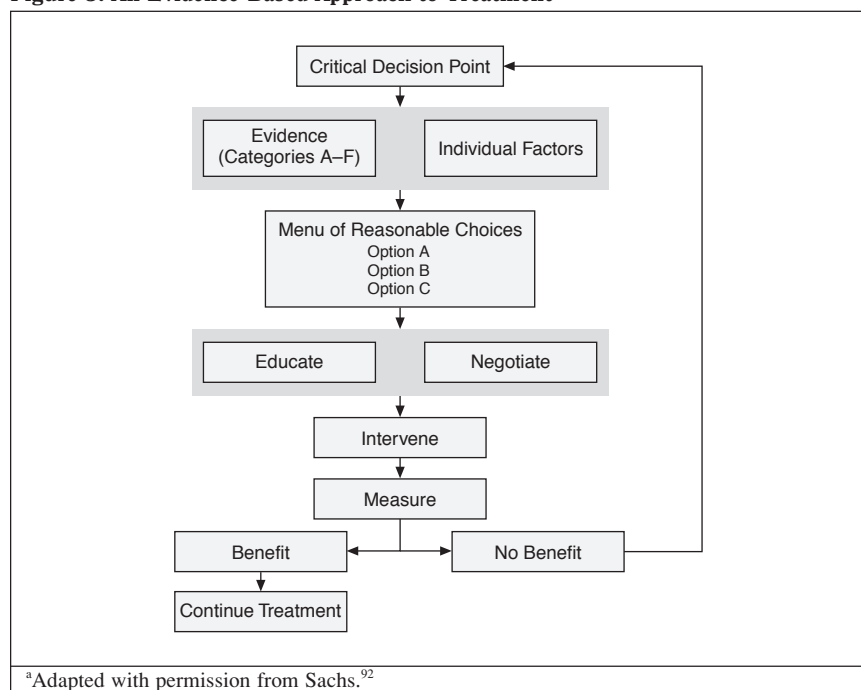
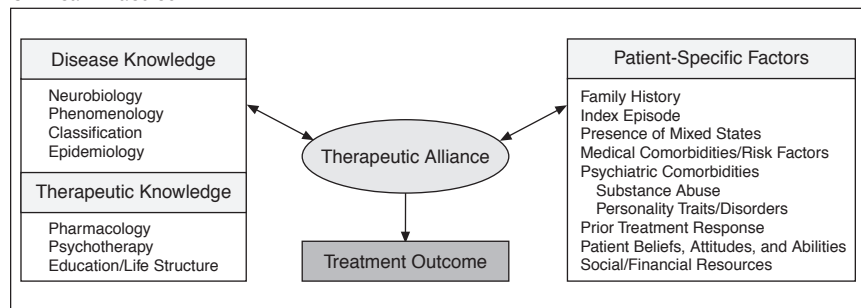
Optimal maintenance treatment should be based on evidence provided in the literature. According to Dr. Gardner, the problem with evidence-based treatment for maintenance therapy for bipolar disorder is that few data exist on which to base individualized maintenance treatment.<sup>85</sup> Most studies are limited to acute phase treat-

ment rather than maintenance treatment,<sup>86-88</sup> and the data on maintenance therapy are largely limited to patients with bipolar I disorder, while the majority of patients with bipolar spectrum disorders do not have classically defined bipolar I disorder.<sup>89</sup> Additionally, the existing research cohorts of bipolar disorder have often excluded adolescents, children, and patients who have comorbid psychiatric or medical conditions. These gaps in the data substantially limit the ability of the clinician to individualize treatment based on specific patient needs.

Treatment guidelines can assist clinicians by summarizing the available data and accepted treatment principles to outline reasonable treatment options. However, Dr. Gardner advised that guidelines are intended only to inform clinical practice, not to take the place of clinical judgment or design a generic treatment protocol for

### The Role of the Therapeutic Alliance in Evidence-Based Medicine

According to Dr. Gardner, an ideal evidence-based clinical practice approach for bipolar maintenance treatment requires a slight modification to the iterative approach detailed by STEP-BD.<sup>91</sup> At the center of the evidence-based approach is the

**Figure 3. An Evidence-Based Approach to Treatment<sup>a</sup>****Figure 4. The Importance of Therapeutic Alliance in Evidence-Based Clinical Practice**

therapeutic alliance between the clinician and the patient (Figure 4). From the first meeting with the patient, treatment should be characterized by active listening on the clinician's part and the identification of the patient's life goals. Patient life goals have bearing on treatment because a person's goals reflect his or her ability to function and quality of life. If patients feel that the clinician is committed to their achievement of life goals, then the patients will actively and positively engage in treatment. Dr. Gardner advised that the clinician should be explicit

with the patient about the fact that the treatment is personalized to each patient. The clinician should focus on the unique aspects of the patient's experience, drawing on the full range of scientific information at the clinician's disposal, and then engage the patient in an ongoing process of self-monitoring and self-management.

#### Maintenance Treatment Goals and Barriers

Guidelines for the treatment of bipolar disorder<sup>85,90</sup> state that the goal of treatment is to seek full remission of

all symptoms and to maintain wellness over time. Dr. Gardner reported that common barriers to full remission in patients with bipolar disorder include mixed states, depressive relapses, and subsyndromal mixed, manic, and depressive symptoms. Mixed states raise the risk of suicidal ideation in patients with bipolar disorder,<sup>22,93</sup> and subsyndromal mixed and manic symptoms often predict syndromal relapse.<sup>77-79</sup> Depressive relapses and subsyndromal depressive symptoms are particularly associated with impaired functioning and impaired quality of life in patients with bipolar disorder.<sup>77,94</sup> Finding ways to seek full remission of symptoms and sustain robust wellness is the ultimate goal of maintenance treatment, since functioning and quality of life are inextricably linked to patient treatment goals.

For maintenance treatment to be successful, attention to safety, tolerability, and treatment adherence is essential; otherwise, patients and clinicians may face poor patient outcomes.<sup>95</sup> Reviews<sup>95-97</sup> of safety and tolerability profiles of bipolar treatments conclude that continued patient monitoring is necessary for both treatment adherence and optimal treatment outcomes.

#### Conclusion

Dr. Gardner closed with the statement that evidence-based medicine is an important tool for bipolar maintenance treatment, although the data concerning the management of patients with bipolar disorder are currently limited and should be increased. Clinicians often develop treatment plans from data sets based on patients who are different from the patients they see in clinical practice. The practice of evidence-based medicine depends on a dynamic clinician-patient alliance, which provides the best possible outcome for patients by individualizing patient treatment and for clinicians by ensuring professional satisfaction.

## What Clinicians Need to Know About Neuroprotective Issues in Bipolar Disorder

According to Vladimir Maletic, M.D., bipolar disorder is a highly recurrent condition associated with substantial functional deficits. Recent epidemiologic studies suggest that repeated mood episodes<sup>98</sup> and minor residual symptoms<sup>12</sup> may increase the risk of future recurrence. Dr. Maletic stated that bipolar disorder may also be a degenerative and progressive condition. Detectable changes in the brain may record past manic, depressive, or mixed episodes. New research is revealing that these changes may be reversible with the help of knowledge gained from neuroimaging and pathohistologic research.

### Neuroimaging Findings in Patients With Bipolar Disorder

The interpretation of neuroimaging studies of bipolar disorder has been complicated by several factors, such as the lack of identification of patient mood states and differences in patient medication status. Despite these difficulties, some observations have been made concerning the effect of bipolar disorder on the brain. Magnetic resonance imaging studies<sup>99,100</sup> indicated that patients who had experienced multiple bipolar episodes had larger lateral ventricles than both healthy controls and patients who had experienced only 1 episode.<sup>100</sup>

Prefrontal cortical abnormalities have also been noted in bipolar disorder. The ventromedial prefrontal cortex (VMPFC) is part of the network that, hypothetically, processes emotionally relevant information to guide behavior.<sup>101</sup> The VMPFC tends to have increased activity in both unipolar<sup>102</sup> and bipolar depression.<sup>103</sup> Researchers have discovered functional and structural changes in the VMPFC of adolescents and young adults with bipolar disorder compared with healthy controls.<sup>103</sup> These differences compromise patients' ability to

adapt to change in emotional and social circumstances.

The lateral orbital prefrontal cortex (LOPFC) appears to have a role in regulating maladaptive and perseverative emotional responses. Activity in the LOPFC appears to be increased during depressive states.<sup>102</sup> Decreased LOPFC metabolism in bipolar manic states may contribute to the disinhibition often seen in manic patients.<sup>104</sup> Decreased activity in the dorsolateral prefrontal cortex (DLPFC) in bipolar disorder may be associated with compromised working memory, impaired ability to sustain attention, and compromised executive function.<sup>105</sup>

The subgenual anterior cingulate cortex (ACC) has a role in assessing the salience of emotional and motivational information and adjusting behavior accordingly. Imaging studies<sup>106</sup> have discovered altered metabolism and size of the subgenual ACC in patients with bipolar disorder compared with healthy controls.

Limbic structures also appear to be affected by bipolar disorder. Findings regarding the size of hippocampus are inconsistent. Some studies comparing patients with bipolar disorder with healthy controls found enlarged hippocampal volume, others a decrease, or, no difference in size.<sup>107</sup> Structural changes in the amygdala may reflect the physical progression of the illness. Adolescents with bipolar disorder appear to have smaller amygdala volume, while adults with bipolar disorder have larger amygdala compared with healthy controls.<sup>108</sup> These findings may suggest a progression over time in abnormal amygdala volumes.

Functional studies<sup>109</sup> have typically found increased activity in the limbic structures of bipolar patients in both manic and depressed states.<sup>109</sup> The amygdala plays a role in rapidly assessing and assigning emotional value to surprising and ambiguous stimuli. Pa-

tients with bipolar disorder tend to have overly intense responses to changes in circumstance and difficulty correctly identifying the meaning of emotional facial expressions.

Several other structures in the brain appear affected by bipolar disorder. Vermal size might be associated with the number of previous bipolar episodes,<sup>107</sup> which is of particular interest since the cerebellar vermis has been implicated in the automatic emotional responses to facial expressions.

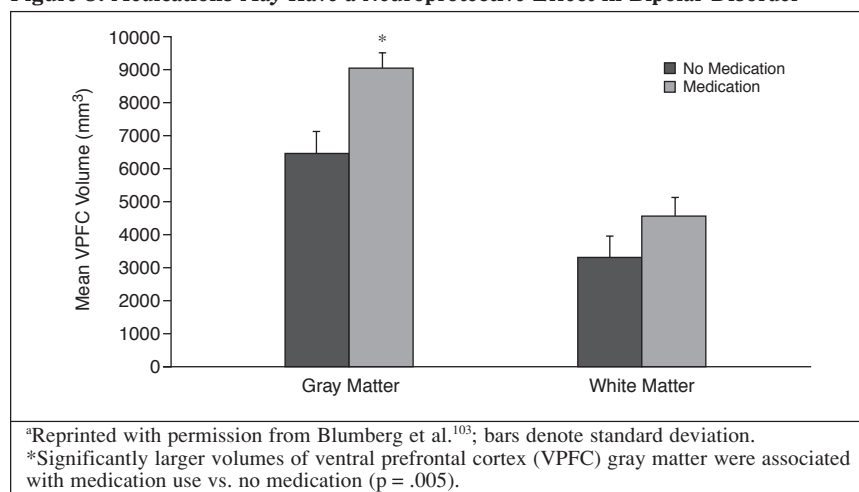
Thus, Dr. Maletic opined that structural and functional changes in the brain support an organic basis for the symptoms of bipolar disorder. In some instances, data suggest a cumulative effect of prior episodes.<sup>107</sup>

### Pathohistologic Findings for Patients With Bipolar Disorder

Pathohistologic research indicates that bipolar disorder is associated with significant cell pathology. Postmortem studies of patients with bipolar disorder have noted a reduction in glial cell numbers and density.<sup>110</sup> Glial pathology has been noted in the subgenual ACC, DLPFC, orbitofrontal cortex, and the amygdala of unmedicated bipolar patients.<sup>111</sup> Distribution of cellular pathology coincides with findings of structural and functional imaging studies and hints at association with clinical manifestations of bipolar illness.<sup>112</sup>

A 16% to 22% decrease in neuronal density in the DLPFC has been observed in bipolar disorder.<sup>113</sup> Patients with bipolar disorder appear to have a higher number of noradrenergic neurons in the locus ceruleus as well as subtle structural deficits of serotonergic neurons in the dorsal raphe.<sup>112</sup>

Dr. Maletic noted that histologic evidence does not support the view of bipolar disorder as a typical neurodegenerative disease. By contrast, conventional neurodegenerative disorders are associated with neuronal loss and prominent gliosis.<sup>112</sup> The relationship between cell pathology and the clinical manifestations of bipolar disorder has yet to be established.

**Figure 5. Medications May Have a Neuroprotective Effect in Bipolar Disorder\***

### Integrating Research Findings Into Clinical Practice

Dr. Maletic proposed that if a relationship between clinical manifestations of bipolar disorder and functional alterations observed in imaging studies exists, then successful treatment of bipolar disorder should be reflected in the normalization of these functional changes. Researchers have found consistent evidence that medications, including lithium<sup>114</sup> and atypical antipsychotics,<sup>115-117</sup> may normalize aberrant patterns of activity in the brain. Neuroimaging also provides indirect but compelling evidence of neu-

rotrophic benefits associated with pharmacotherapy. Mood-stabilizing agents may aid neurogenesis and exercise neuroprotective effects in the brain (Figure 5).<sup>98,107</sup> In addition to providing clinical improvement and normalization of function, successful treatment may preserve the brain's neural structure. Dr. Maletic conceded that these conclusions are tentative, and he called for systematic correlative studies to establish the connection between clinical improvement of bipolar illness and normalization of brain structure and function in imaging studies.

After the acute episode is stabilized, the clinician should transition the patient to maintenance treatment. Dr. Jain reiterated that the dangers of less-than-optimum maintenance treatment include high relapse and recurrence rates, reduced patient compliance, and adverse neurobiological events. Many pharmacologic and nonpharmacologic maintenance treatment options are available for patients. Dr. Jain encouraged clinicians to look for information about medications in guidelines from prominent scientific bodies, expert consensus opinions, and published research literature to aid decision-making for bipolar maintenance treatment, although unique patient factors must be considered. While patient compliance is important for treatment success, Dr. Jain said that clinician compliance with recommended treatment strategies is also vital. A recent survey<sup>118</sup> of psychiatrists revealed that only 64% reported routinely using any treatment guidelines, and less than 20% reported using APA guidelines<sup>55</sup> for the treatment of bipolar disorder. Dr. Jain also recommended the use of daily mood ratings to track the progress of patient treatment, such as the Bipolar Monthly Mood Chart. Maintaining daily mood ratings is useful for both patients and clinicians in catching relapses early.<sup>119</sup>

Dr. Jain listed several general rules that apply to the maintenance treatment of bipolar disorder.

### Conclusion: Diagnosis of Acute Bipolar States, Stabilization, and Maintenance Treatments

Dr. Jain drew several conclusions from the presentations on the management of bipolar disorder from urgent situations to maintenance therapy. He stated that bipolar disorder is a common problem, and psychiatrists and non-psychiatrists alike face urgent situations in clinical practice. Many stakeholders have a vested interest in optimizing patient outcomes, including patients themselves, their families and caregivers, their employers, and society at large. Bipolar disorder can not only cause loss

of life through suicide and other mortality but can also lead to family dysfunction and occupational and educational disruption.<sup>2</sup> Therefore, urgently ill patients with bipolar disorder need quick and efficient stabilization. Acute episode management requires accurate diagnosis of the patient's mood state, an assessment of the likelihood of self-harm or harm to others, use of interventions that work rapidly but are also safe and tolerable, and implementation of psychoeducation.

- Maintenance treatment should be offered routinely, because relapse is the rule in bipolar disorder.
- Multiple factors should be considered when prescribing pharmacotherapy, including the patient's individual needs, the efficacy and side effect burden of individual medications, the availability and quality of maintenance treatment data, and FDA indications.
- All guidelines agree that the use of antidepressants should be avoided.

- While monotherapy mood stabilizer treatment is preferred, combination therapy is indicated if treatment response is suboptimum.
- A number of effective pharmacologic treatment options are available for maintenance treatment, such as lithium, valproate, lamotrigine, carbamazepine, oxcarbazepine, and atypical antipsychotics, which can be used as monotherapy or as part of combination therapy.
- Various forms of psychotherapy, such as group psychoeducation, family-focused therapy, interpersonal and social rhythm therapy, and cognitive-behavioral therapy have become increasingly well studied and are indicated for the majority of patients as adjunctive treatments.<sup>120</sup>

Dr. Jain stated that, despite widespread recognition for the need for maintenance treatment, clinicians are still far from offering most patients life-long prophylaxis. Clinicians now have access to multiple tools that ensure optimum maintenance for patients. Carefully matching an individual patient's needs with specific interventions is the ideal path to achieving high rates of success.

**Drug names:** aripiprazole (Abilify), carbamazepine (Carbatrol, Equetro, and others), chlorpromazine (Sonazine, Thorazine, and others), clozapine (Clozaril, FazaClo, and others), divalproex sodium (Depakote), haloperidol (Haldol and others), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), lorazepam (Ativan and others), olanzapine (Zyprexa, Zyprexa Zydis), olanzapine-fluoxetine (Symbyax), oxcarbazepine (Trileptal), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

**Disclosure of off-label usage:** The chair has determined that, to the best of his knowledge, clozapine is not approved by the U.S. Food and Drug Administration for the treatment of bipolar disorder; haloperidol, lorazepam, and intramuscular ziprasidone are not approved for agitation in bipolar disorder; lamotrigine is not approved for acute episode treatment; and the maximum FDA-approved dose for olanzapine is 20 mg p.o. twice daily.

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**Answer to Pretest: 1. a**

## ACADEMIC HIGHLIGHTS

pp. 367–380

### 1. According to Jain, patients with bipolar disorder are at a high risk for:

- a. Suicide
- b. Lost work days
- c. Marital discord
- d. All of the above

### 2. Manning stated that mixed states:

- a. Have been best defined by the DSM-IV-TR
- b. Pose less risk for suicide than pure manic states
- c. Are easily distinguished from other psychiatric illnesses
- d. May be exacerbated by inappropriate medication

### 3. Garlow characterized the treatment goal for an acute bipolar mood episode as 2-fold: first, the patient's symptoms must be rapidly relieved, and, second, the clinician should successfully transition the patient into maintenance therapy.

- a. True
- b. False

### 4. Jackson explained that *concordance* is:

- a. Synonymous with *adherence*
- b. The degree to which the patient and clinician view the illness and its treatment in the same way
- c. The model of the therapeutic alliance in which the clinician is paternalistic
- d. None of the above

### 5. Gardner stated that, if maintenance therapy is effective, all of the following should occur *except*:

- a. Subsyndromal symptoms will be reduced
- b. Functioning and quality of life will be improved
- c. Treatment can be discontinued
- d. Relapse will be prevented



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