Managing Bipolar Disorder From Urgent Situations to Maintenance Therapy

This 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."[1] 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).[2] Clinicians have long been aware of the common occurrence of aggression and agitation in unstable patients with bipolar disorder.[3] The National Comorbidity Survey (NCS)[4] and the Epidemiologic Catchment Area Survey[5] 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.[6]

Bipolar disorder is also associated with severe impairment of social, vocational, and cognitive functioning.[7] Dr. Jain noted that relationships and marriages are adversely affected when a partner suffers from bipolar disorder. For example, evidence[8] 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,[9] 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[10] that found that 69% of patients with bipolar disorder were initially misdiagnosed. Another study[11] 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)[12] 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[13] 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 nonpharmacologic 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 patient outcomes, keeping in mind that problems can arise due to medication noncompliance[14] or unnecessary or ineffective treatments.[15] 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.[16] 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)[17] 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,[18] or a depressive mixed state, which is major depression combined with 3 or more hypomanic symptoms.[19] In the concept of trait mixing,[20] 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[21,22] 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,[10] employment disruptions,[23] involvement with the legal system,[23] and high utilization of medical resources.[24]

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[11,25] 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[a]
Severe agitation[a]
Refractory anxiety[a]
Unendurable sexual excitement[a]
Intractable insomnia[a]
Suicidal obsession and impulses
Histrionic demeanor
Genuine, intense suffering

[a]Based on Akiskal and Mallya.[28]

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.[26] In addition, patients in mixed states often report refractory insomnia and suicidal tendencies, leading clinicians to overmedicate patients with sedative hypnotics.[27] To prevent misdiagnosis, Akiskal and Mallya[28] 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.

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[29] 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 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[30] 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[31] and aripiprazole[32] 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[33] 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[34] has been the standard medication for manic episodes in bipolar disorder. Effective, FDA-approved treatments for acute mania are the conventional antipsychotic chlorpromazine,[35] divalproex sodium,[36] and extended-release carbamazepine.[37] Oral formulations of risperidone,[38] olanzapine,[31] ziprasidone,[33] quetiapine,[41] and aripiprazole[32] are all indicated for new-onset manic episodes.

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[32]	✓[a]	✓	✓		✓
Carbamazepine[37]		✓[a]	✓[a]		
Chlorpromazine[35]		✓			
Divalproex[36]		✓[a]	✓[a]		
Lamotrigine[42]					✓
Lithium[34]		✓			✓
Olanzapine[31]	✓[a]	✓	✓		✓
Olanzapine-fluoxetine[39]				✓	
Quetiapine[41]		✓		✓	
Risperidone[38]		✓	✓		
Ziprasidone[33]		✓	✓		

[a]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,[38] olanzapine,[31] ziprasidone,[33] aripiprazole,[32] and the extended-release formulations of both carbamazepine[37] and divalproex sodium.[36] (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[39] and quetiapine[40,41] 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[43] for a short time. Although antidepressants can be effective short-term treatments for bipolar depression,[44,45] 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.[46,47] 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.[45]

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.[48] 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.[49,50] For manic episodes, risperidone,[38] olanzapine,[31] and quetiapine[40] are all indicated for use with the maintenance treatments lithium and divalproex sodium. Risperidone[38] and olanzapine[31] 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,[39] quetiapine,[40] a mood stabilizer, such as lamotrigine,[42] or an antidepressant.[50–53]

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

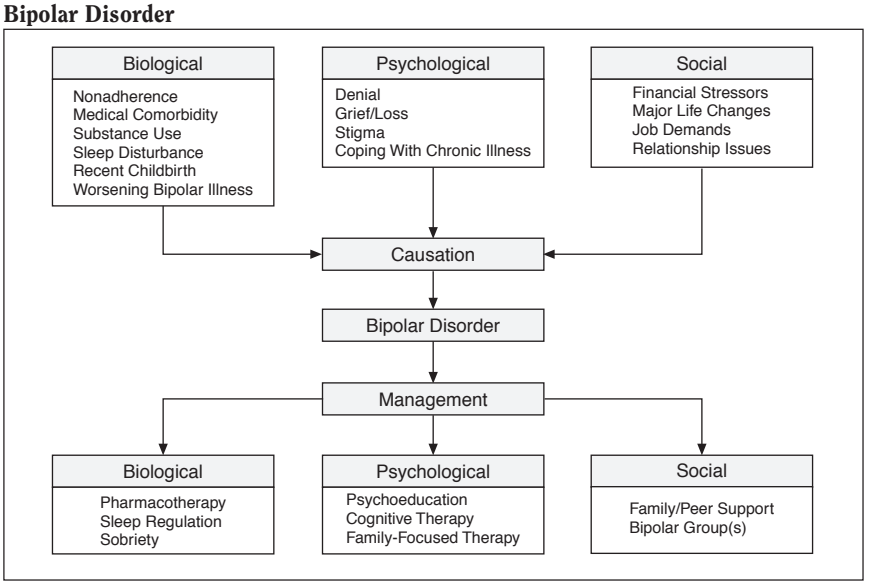
Biological, psychological, and social factors affect the development and the treatment of acute bipolar states. Dr. Skale presented the biopsychosocial model to illustrate patient issues that can precipitate or be symptomatic of a bipolar urgent situation and proposed management strategies to optimally 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,[54,55] 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[56] 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[57] and family-focused therapy[58] 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[23]; however, partial hospitalization, referral to a crisis stabilization center, and intensified contact with mental health care professionals[58] 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[54,55]:

- 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.[54] 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.[55]

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)[55] because of the risk of acute dystonic reactions.

According to the APA,[55] 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[55] 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.[54,55] 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.[59] 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.[60]

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.[61,62] In addition, postpartum patients are at high risk for relapse into mania, depression, or psychosis, with a relapse rate as high as 50%.[63]

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.

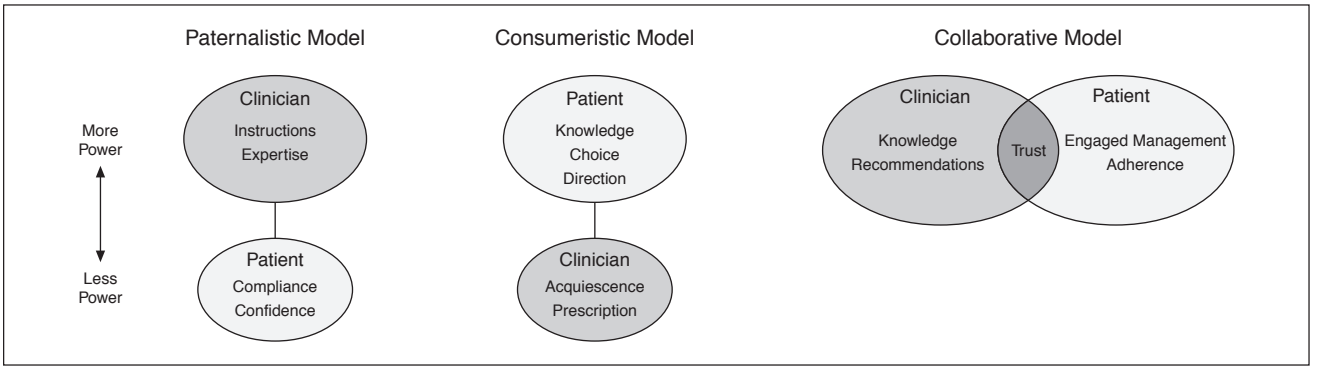
Facilitating Adherence in Maintenance Therapy

The goals of therapy differ according to the phase in which the patient presents,[64] 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,[54] the lag between symptomatic and functional recovery,[65] medical and psychiatric comorbidities,[66,67] and suboptimal quality of care.[68]

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,[69] 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.[70] 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.[71] 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.[71] 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.[72]

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 believe 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,[73,74] consumeristic,[75] and collaborative[76] models of the therapeutic alliance (Figure 2). In the paternalistic model,[73,74] 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,[75] 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,[76] 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.[72] 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.

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,[17,77–79] treating bipolar disorder requires more than just stabilization of the acute episode. Effective maintenance can prevent relapse[80,81–83]; reduce subsyndromal symptoms; decrease hospitalizations, morbidity, and mortality[84]; 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.[85] Most studies are limited to acute phase treatment rather than maintenance treatment,[86–88] 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.[89] 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.

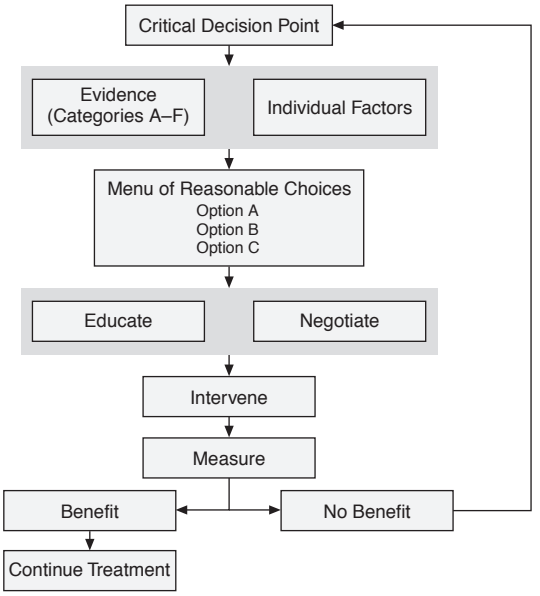
Treatment guidelines can assist clinicians by summarizing the available data and accepted treatment principles to outline reasonable treatment options. However, Dr. Gardner advised that guidelines are intended only to inform clinical practice, not to take the place of clinical judgment or design a generic treatment protocol for 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,[85] the Expert Consensus Guideline Series,[90] and STEP-BD[91] 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.[91] 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).[92] At each critical decision point, such as an acute manic or mixed state, clinicians develop a menu of reasonable treatment options.[91] 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[91] 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.

The Role of the Therapeutic Alliance in Evidence-Based Medicine

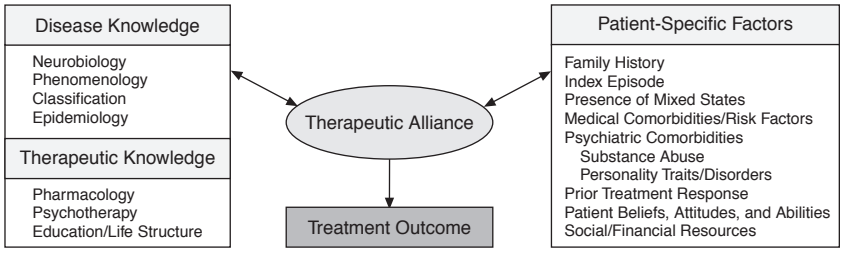
According to Dr. Gardner, an ideal evidence-based clinical practice approach for bipolar maintenance treatment requires a slight modification to the iterative approach detailed by STEP-BD.[91] At the center of the evidence-based approach is the

Figure 3. An Evidence-Based Approach to Treatment[a]



[a]Adapted with permission from Sachs.[92]

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[85,90] 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,[22,93] and subsyndromal mixed and manic symptoms often predict syndromal relapse.[77–79] Depressive relapses and subsyndromal depressive symptoms are particularly associated with impaired functioning and impaired quality of life in patients with bipolar disorder.[77,94] 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.[95] Reviews[95–97] 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[98] and minor residual symptoms[12] 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[99,100] 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.[100]

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.[101] The VMPFC tends to have increased activity in both unipolar[102] and bipolar depression.[103] Researchers have discovered functional and structural changes in the VMPFC of adolescents and young adults with bipolar disorder compared with healthy controls.[103] 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.[102] Decreased LOPFC metabolism in bipolar manic states may contribute to the disinhibition often seen in manic patients.[104] 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.[105]

The subgenual anterior cingulate cortex (ACC) has a role in assessing the salience of emotional and motivational information and adjusting behavior accordingly. Imaging studies[106] 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.[107] 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.[108] These findings may suggest a progression over time in abnormal amygdala volumes.

Functional studies[109] have typically found increased activity in the limbic structures of bipolar patients in both manic and depressed states.[109] The amygdala plays a role in rapidly assessing and assigning emotional value to surprising and ambiguous stimuli. Patients 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,[107] 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.[107]

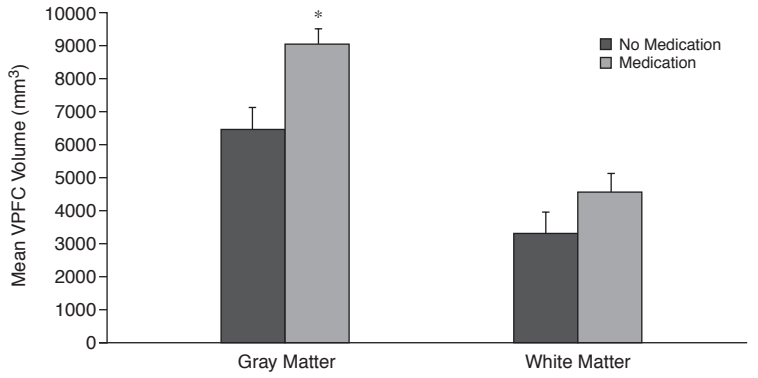
Pathohistologic Findings for Patients With Bipolar Disorder

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.[110] Glial pathology has been noted in the subgenual ACC, DLPFC, orbitofrontal cortex, and the amygdala of unmedicated bipolar patients.[111] Distribution of cellular pathology coincides with findings of structural and functional imaging studies and hints at association with clinical manifestations of bipolar illness.[112]

A 16% to 22% decrease in neuronal density in the DLPFC has been observed in bipolar disorder.[113] 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 raphae.[112]

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.[112] 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[a]



[a]Reprinted with permission from Blumberg et al.[103]; bars denote standard deviation.
*Significantly larger volumes of ventral prefrontal cortex (VPFC) gray matter were associated with medication use vs. no medication (p = .005).

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[114] and atypical antipsychotics,[115–117] may normalize aberrant patterns of activity in the brain. Neuroimaging also provides indirect but compelling evidence of neurotrophic benefits associated with pharmacotherapy. Mood-stabilizing agents may aid neurogenesis and exercise neuroprotective effects in the brain (Figure 5).[98,107] 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.

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 nonpsychiatrists 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.[2] 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.

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[118] of psychiatrists revealed that only 64% reported routinely using any treatment guidelines, and less than 20% reported using APA guidelines[55] 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.[119]

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

- 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.[120]

Dr. Jain stated that, despite widespread recognition for the need for maintenance treatment, clinicians are still far from offering most patients lifelong 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.

REFERENCES

1. Merriam-Webster's Collegiate Dictionary, Tenth Edition. Springfield, Mass: Merriam-Webster, Inc; 2002
2. Dutta R, Boydell J, Kennedy N, et al. Suicide and other causes of mortality in bipolar disorder: a longitudinal study. Psychol Med 2007:1–9. doi:10.1017/S0033291707000347
3. Feldmann TB. Bipolar disorder and violence. Psychiatr Q 2001;72:119–129
4. Corrigan PW, Watson AC. Findings from the National Comorbidity Survey on the frequency of violent behavior in individuals with psychiatric disorders. Psychiatry Res 2005;136:153–162
5. Swanson JW, Holzer CEI, Ganju VK, et al. Violence and psychiatric disorder in the community: evidence from the Epidemiologic Catchment Area surveys. Hosp Community Psychiatry 1990;41:761–770
6. Quanbeck CD, McDermott BE, Frye MA. Clinical and legal characteristics of inmates with bipolar disorder. Curr Psychiatry Rep 2005;7: 478–484
7. Huxley N, Baldessarini RJ. Disability and its treatment in bipolar disorder patients. Bipolar Disord 2007;9:183–196
8. Lam D, Donaldson C, Brown Y, et al. Burden and marital and sexual satisfaction in the partners of bipolar patients. Bipolar Disord 2005;7:431–440
9. Kessler RC, Akiskal HL, Ames M, et al. Prevalence and effects of mood disorders on work performance in a nationally representative sample of US workers. Am J Psychiatry 2006;163:1561–1568
10. Hirschfeld RM, Lewis L, Vornik LA. Perceptions and impact of bipolar disorder: how far have we really come? results of the National Depressive and Manic-Depressive Association 2000 survey of individuals with bipolar disorder. J Clin Psychiatry 2003;64:161–174
11. Hirschfeld RM, Cass AR, Holt DC, et al. Screening for bipolar disorder in patients treated for depression in a family medicine clinic. J Am Board Fam Pract 2005;18:233–239
12. Perlis RH, Ostacher MJ, Patel JK, et al. Predictors of recurrence in bipolar disorder: primary outcomes from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Am J Psychiatry 2006;163:217–224
13. Kraepelin E. Manic-Depressive Insanity and Paranoia. Edinburgh, Scotland: E & S Livingstone; 1921
14. Reilly-Harrington N, Sachs GS. Psychosocial strategies to improve concordance and adherence in bipolar disorder. J Clin Psychiatry 2006;67: e04
15. Vieta E, Rosa AR. Evolving trends in the long-term treatment of bipolar disorder. World J Biol Psychiatry 2007;8:4–11
16. Akiskal HS. The dark side of bipolarity: detecting bipolar depression in its pleomorphic expressions. J Affect Disord 2005;84:107–115
17. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000
18. McElroy SL, Strakowski SM, Keck PE Jr, et al. Differences and similarities in mixed and pure mania. Compr Psychiatry 1995;36:187–194
19. Benazzi F. Mixed states in bipolar II disorder: should full hypomania always be required? Psychiatry Res 2004;127:247–257
20. Perugi G, Akiskal HS. Emerging concepts of mixed states: a longitudinal perspective. In: Marneros A, Goodwin F, eds. Bipolar Disorders: Mixed States, Rapid Cycling, and Atypical Forms. Cambridge, England: Cambridge University Press; 2005:45–60
21. Dilsaver SC, Chen YW, Swann AC, et al. Suicidality in patients with pure and depressive mania. Am J Psychiatry 1994;151:1312–1315
22. Strakowski SM, McElroy SL, Keck PE Jr, et al. Suicidality among patients with mixed and manic bipolar disorder. Am J Psychiatry 1996;153:674–676
23. Calabrese JR, Hirschfeld RMA, Reed M, et al. Impact of bipolar disorder on a US community sample. J Clin Psychiatry 2003;64:425–432
24. Bryant-Comstock L, Stender M, Devercelli G. Health care utilization and costs among privately insured patients with bipolar I disorder. Bipolar Disord 2002;4:398–405
25. Manning JS, Haykal RF, Connor PD, et al. On the nature of depressive and anxious states in a family practice setting: the high prevalence of bipolar II and related disorders in a cohort followed longitudinally. Compr Psychiatry 1997;38:102–108
26. Ghaemi SN, Hsu DJ, Soldani F, et al. Antidepressants in bipolar disorder: the case for caution. Bipolar Disord 2003;5:421–433
27. Baldessarini RJ, Leahy L, Arcona S, et al. Patterns of psychotropic drug prescriptions for US patients with diagnoses of bipolar disorders. Psychiatr Serv 2007;58:85–91
28. Akiskal HS, Mallya G. Criteria for the "soft" bipolar spectrum: treatment implications. Psychopharmacol Bull 1987;23:68–73
29. Valtonen H, Suominen K, Mantere O, et al. Suicidal ideation and attempts in bipolar I and II disorders. J Clin Psychiatry 2005;66:1456–1462
30. Haldol (haloperidol). Physicians's Desk Reference. 57th ed. Montvale, NJ: Thomson PDR; 2003
31. Zyprexa [package insert]. Indianapolis, Ind: Eli Lilly and Company; 2006. Available at: http://pi.lilly.com/us/zyprexa-pi.pdf. Accessed April 17, 2007
32. Abilify [package insert]. Tokyo, Japan: Otsuka America Pharmaceutical, Inc; 2006. Available at: http://www.otsuka.com/documents/AbilifyFullPI.pdf. Accessed June 6, 2007
33. Geodon (ziprasidone). Physicians' Desk Reference. 61st ed. Montvale, NJ: Thomson PDR; 2007
34. Eskalith (lithium carbonate). Physicians' Desk Reference. 60th ed. Montvale, NJ: Thomson PDR; 2006
35. Thorazine (chlorpromazine). Physicians' Desk Reference. 57th ed. Montvale, NJ: Thomson PDR; 2003
36. Depakote ER divalproex sodium extended-release tablets [package insert]. North Chicago, Ill: Abbott Laboratories; 2006. Available at: http//www.rxabbott.com/pdf/dep3.pdf. Accessed May 17, 2007
37. Equetro TM (carbamazepine) extended-release capsules [package insert]. Wayne, PA: Shire US Inc; 2005. Available at http://www.fda.gov/cder/foi/label/2006/021710s003lbl.pdf. Accessed May 17, 2007
38. Risperdal [package insert]. Titusville, NJ: Janssen; 2006. Available at: http://www.risperdal.com/risperdal/shared/risperdal.pdf. Accessed April 17, 2007
39. Symbyax (olanzapine-fluoxetine). Physicians' Desk Reference. 61st ed. Montvale, NJ: Thomson PDR; 2007
40. Seroquel [package insert]. Wilmington, Del: AstraZeneca Pharmaceuticals; 2006. Available at: http://www.astrazeneca-us.com/pi/

seroquel.pdf. Accessed Jan 31, 2007
41. Seroquel (quetiapine). Physicians' Desk Reference. 61st ed. Montvale, NJ: Thomson PDR; 2007
42. Lamictal [package insert]. Greenville, NC: GlaxoSmithKline; 2005. Available at: http://www.fda.gov/cder/foi/label/2006/020241s10s21s25s26s27,020764s3s14s18s19s20lbl.pdf. Accessed May 17, 2007
43. Malhi GS, Mitchell PB, Salim S. Bipolar depression: management options. CNS Drugs 2003;17:9–25
44. Post RM, Leverich GS, Nolen WA, et al. A re-evaluation of the role of antidepressants in the treatment of bipolar depression: data from the Stanley Foundation Bipolar Network. Bipolar Disord 2003;5:396–406
45. Gijsman HJ, Geddes JR, Rendell JM, et al. Antidepressants for bipolar depression: a systematic review of randomized, controlled trials. Am J Psychiatry 2004;161:1537–1547
46. Leverich GS, Altshuler LL, Frye MA, et al. Risk of switch in mood polarity to hypomania or mania in patients with bipolar depression during acute and continuation trials of venlafaxine, sertraline, and bupropion as adjuncts to mood stabilizers. Am J Psychiatry 2006;163:232–239
47. Altshuler LL, Suppes T, Black DO, et al. Lower switch rate in depressed patients with bipolar II than bipolar I disorder treated adjunctively with second-generation antidepressants. Am J Psychiatry 2006;163:313–315
48. Daban C, Colom F, Sanchez-Moreno J, et al. Clinical correlates of first-episode polarity in bipolar disorder. Compr Psychiatry 2006;47:433–437
49. Gajwani P, Kemp DE, Muzina DJ, et al. Acute treatment of mania: an update on new medications. Curr Psychiatry Rep 2006;8:504–509
50. Keck PE Jr. Evaluation and management of breakthrough depressive episodes. J Clin Psychiatry 2004;65(suppl 10):11–15
51. Young LT, Joffe RT, Robb JC, et al. Double-blind comparison of addition of a second mood stabilizer versus an antidepressant to an initial mood stabilizer for treatment of patients with bipolar depression. Am J Psychiatry 2000;157:124–126
52. Gyulai L, Bowden CL, McElroy SL, et al. Maintenance efficacy of divalproex in the prevention of bipolar depression. Neuropsychopharmacology 2003;28:1374–1382
53. Redmond JR, Jamison KL, Bowden CL. Lamotrigine combined with divalproex or lithium for bipolar disorder: a case series. CNS Spectr 2006;11:915–918
54. Goodwin FK, Jamison KR. Manic-Depressive Illness. New York, NY: Oxford University Press; 1990
55. American Psychiatric Association. Practice Guideline for the Treatment of Patients with Bipolar Disorder [Revision]. Am J Psychiatry 2002;159(suppl 4):1–50
56. Colom F, Vieta E, Martinez-Arán A, et al. A randomized trial on the efficacy of group psychoeducation in the prophylaxis of recurrences in bipolar disorder whose disease is in remission. Arch Gen Psychiatry 2003;60:402–407
57. Lam DH, Watkins ER, Hayward P, et al. A randomized controlled study of cognitive therapy for relapse prevention for bipolar disorder: outcome of the first year. Arch Gen Psychiatry 2003;60:145–152
58. Miklowitz DJ, Richards JA, George EL, et al. Integrated family and individual therapy for bipolar disorder: results of a treatment development study. J Clin Psychiatry 2003;64:182–191
59. Regier DA, Farmer ME, Rae DS, et al. Comorbidity of mental disorders with alcohol and other drug abuse: results from the Epidemiologic Catchment Area (ECA) Study. JAMA 1990;264:2511–2518
60. Sonne SC, Brady KT. Substance abuse and bipolar comorbidity. Psychiatr Clin North Am 1999;22:609–627
61. Wyszynski DF, Nambisan M, Surve T, et al. Increased rate of major malformations in offspring exposed to valproate during pregnancy. Neurology 2005;64:961–965
62. Tatum WO. In utero antiepileptic drug exposure. Expert Rev Neurother 2006;6:1785–1787
63. Altshuler LL, Hendrick V, Cohen LS. Course of mood and anxiety disorders during pregnancy and the postpartum period. J Clin Psychiatry 1998;59(suppl 2):29–33
64. Swann AC. Long-term treatment in bipolar disorder. J Clin Psychiatry 2005;66(suppl 1):7–12
65. Keck PE Jr, McElroy SL, Strakowski SM, et al. 12-month outcome of patients with bipolar disorder following hospitalization for a manic or mixed episode. Am J Psychiatry 1998;155:646–652
66. McElroy SL, Altshuler LL, Suppes T, et al. Axis I psychiatric comorbidity and its relationship to historical illness variables in 288 patients with bipolar disorder. Am J Psychiatry 2001;158:420–426
67. McIntyre RS, Konarski JZ, Yatham LN. Comorbidity in bipolar disorder: a framework for rational treatment selection. Hum Psychopharmacol 2004;19:369–386
68. Kilbourne AM, Pincus HA. Patterns of psychotropic medication use by race among veterans with bipolar disorder. Psychiatr Serv 2006;57:123–126
69. Rosa AR, Marco M, Fachel JM, et al. Correlation between drug treatment adherence and lithium treatment attitudes and knowledge by bipolar patients. Prog Neuropsychopharmacol Biol Psychiatry 2007;31:217–224
70. Lew KH, Chang EY, Rajagopalan K, et al. The effect of medication adherence on health care utilization in bipolar disorder. Manag Care Interface 2006;19:41–46
71. Carder PC, Vuckovic N, Green CA. Negotiating medications: patient perceptions of long-term medication use. J Clin Pharm Ther 2003;28:409–417
72. Strauss JL, Johnson SL. Role of treatment alliance in the clinical management of bipolar disorder: stronger alliances prospectively predict fewer manic symptoms. Psychiatry Res 2006;145:215–223
73. Friberg F, Scherman MH. Can a teaching and learning perspective deepen understanding of the concept of compliance? a theoretical discussion. Scand J Caring Sci 2005;19:274–279
74. Bassford HA. The justification of medical paternalism. Soc Sci Med 1982;16:731–739
75. Bloomer JS. The consumer of therapy in mental health. Am J Occup Ther 1978;32:621–627
76. Sajatovic M, Davies M, Bauer MS, et al. Attitudes regarding the collaborative practice model and treatment adherence among individuals with bipolar disorder. Compr Psychiatry 2005;46:272–277
77. Judd LL, Akiskal HS, Maser JD, et al. A prospective 12-year study of subsyndromal and syndromal depressive symptoms in unipolar major depressive disorders. Arch Gen Psychiatry 1998;55:694–700
78. Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry 2002;59:530–537
79. Paykel ES, Abbott R, Morriss R, et al. Subsyndromal and syndromal symptoms in the longitudinal course of bipolar disorder. Br J Psychiatry 2006;189:118–123
80. Muzina DJ, Calabrese JR. Maintenance therapies in bipolar disorder: focus on randomized controlled trials. Aust N Z J Psychiatry 2005;39:652–661
81. Calabrese JR, Goldberg JF, Ketter TA, et al. Recurrence in bipolar I disorder: a post hoc analysis excluding relapses in two double-blind maintenance studies. Biol Psychiatry 2006;59:1061–1064
82. McCormack PL, Wiseman LR. Spotlight on olanzapine in bipolar I disorder. CNS Drugs 2005;19:553–555
83. Lin D, Mok H, Yatham LN. Polytherapy in bipolar disorder. CNS Drugs 2006;20:29–42
84. Angst F, Stassen HH, Clayton PJ, et al. Mortality of patients with mood disorders: follow-up over 34–38 years. J Affect Disord 2002;68:167–181
85. Suppes T, Dennehy EB, Hirschfeld RMA, et al. The Texas implementation of medication algorithms: update to the algorithms for treatment of bipolar I disorder. J Clin Psychiatry 2005;66:870–886
86. Kemp DE, Gilmer WS, Fleck J, et al. Aripiprazole augmentation in treatment-resistant bipolar depression: early response and development of akathisia. Prog Neuropsychopharmacol Biol Psychiatry 2007;31:574–577
87. McElroy SL, Suppes T, Frye MA, et al. Open-label aripiprazole in the treatment of acute bipolar depression: a prospective pilot trial. J Affect Disord 2007;101:275–281
88. Endicott J, Rajagopalan K, Minkwitz M, et al. A randomized, double-blind, placebo-controlled study of quetiapine in the treatment of bipolar I and II depression: improvements in quality of life. Int Clin Psychopharmacol 2007;22:29–37
89. Akiskal HS, Bourgeois ML, Angst J, et al. Re-evaluating the prevalence of and diagnostic composition within the broad clinical spectrum of bipolar disorders. J Affect Disord 2000;59(suppl 1):S5–S30
90. Keck PE Jr, Perlis RH, Otto MW, et al. The Expert Consensus Guideline Series: Treatment of Bipolar Disorder 2004. Postgrad Med Special Report 2004:1–120
91. Sachs GS, Thase ME, Otto MW, et al. Rationale, design, and methods of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Biol Psychiatry 2003;53:1028–1042
92. Sachs GS. Implementing evidence-based treatment of manic and mixed episodes. J Clin Psychiatry 2006;67(suppl 11):12–17
93. Goldberg JF, Garno JL, Leon AC, et al. Association of recurrent suicidal ideation with nonremission from acute mixed mania. Am J Psychiatry 1998;155:1753–1755
94. Altshuler LL, Post RM, Black DO, et al. Subsyndromal depressive symptoms are associated with functional impairment in patients with bipolar disorder: results of a large, multisite study. J Clin Psychiatry 2006;67:1551–1560
95. Marken PA, Pies RW. Emerging treatments for bipolar disorder: safety and adverse effect profiles. Ann Pharmacother 2006;40:276–285
96. Dunner DL. Safety and tolerability of emerging pharmacological treatments for bipolar disorder. Bipolar Disord 2005;7:307–325
97. Nemeroff CB. Safety of available agents used to treat bipolar disorder: focus on weight gain.

J Clin Psychiatry 2003;64:532–539
98. Angst J, Gamma A, Sellaro R, et al. Recurrence of bipolar disorders and major depression: a life-long perspective. Eur Arch Psychiatry Clin Neurosci 2003;253:236–240
99. Strakowski SM, DelBello MP, Zimmerman ME, et al. Ventricular and periventricular structural volumes in first- versus multiple-episode bipolar disorder. Am J Psychiatry 2002;159:1841–1847
100. Brambilla P, Harenski K, Nicoletti M, et al. MRI study of posterior fossa structures and brain ventricles in bipolar patients. J Psychiatr Res 2001;35:313–322
101. Manji HK, Drevets WC, Charney DS. The cellular neurobiology of depression. Nat Med 2001;7:541–547
102. Killgore WD, Yurgelun-Todd DA. Ventromedial prefrontal activity correlates with depressed mood in adolescent children. Neuroreport 2006;17:167–171
103. Blumberg HP, Krystal JH, Bansal R, et al. Age, rapid-cycling, and pharmacotherapy effects on ventral prefrontal cortex in bipolar disorder: a cross-sectional study. Biol Psychiatry 2006;59:611–618
104. Altshuler LL, Bookheimer SY, Townsend J, et al. Blunted activation in orbitofrontal cortex during mania: a functional magnetic resonance imaging study. Biol Psychiatry 2005;58:763–769
105. Gruber SA, Rogowska J, Yurgelun-Todd DA. Decreased activation of the anterior cingulate in bipolar patients: an fMRI study. J Affect Disord 2004;82:191–201
106. Drevets WC, Öngür D, Price JL. Neuroimagery abnormalities in the subgenual prefrontal cortex: implications for the pathophysiology of familial mood disorders. Mol Psychiatry 1998;3:220–226
107. Beyer JL, Krishnan KR. Volumetric brain imaging findings in mood disorders. Bipolar Disord 2002;4:89–104
108. Blumberg HP, Fredericks C, Wang F, et al. Preliminary evidence for persistent abnormalities in amygdala volumes in adolescents and young adults with bipolar disorder. Bipolar Disord 2005;7:570–576
109. Blumberg HP, Donegan NH, Sanislow CA, et al. Preliminary evidence for medication effects on functional abnormalities in the amygdala and anterior cingulate in bipolar disorder. Psychopharmacology (Berl) 2005;183:308–313
110. Öngür D, Drevets WC, Price JL. Glial reduction in the subgenual prefrontal cortex in mood disorders. Proc Natl Acad Sci U S A 1998;95:13290–13295
111. Gray NA, Zhou R, Du J, et al. The use of mood stabilizers as plasticity enhancers in the treatment of neuropsychiatric disorders. J Clin Psychiatry 2003;64(suppl 5):3–17
112. Harrison P. The neuropathology of primary mood disorder. Brain 2002;125:1428–1449
113. Rajkowska G, Halaris A, Selemon LD. Reductions in neuronal and glial density characterize the dorsolateral prefrontal cortex in bipolar disorder. Biol Psychiatry 2001;49:741–752
114. Bearden CE, Thompson PM, Dalwani M, et al. Greater cortical gray matter density in lithium-treated patients with bipolar disorder. Biol Psychiatry 2007;62:7–16
115. Atmaca M, Yildirim H, Ozdemir E, et al. Hippocampal ^{1}H MRS in patients with bipolar disorder taking valproate versus valproate plus quetiapine. Psychol Med 2007;37:121–129
116. Moore CM, Biederman J, Wozniak J, et al. Mania, glutamate/glutamine and risperidone in pediatric bipolar disorder: a proton magnetic resonance spectroscopy study of the anterior cingulate cortex. J Affect Disord 2007;99:19–25
117. DelBello MP, Cecil KM, Adler CM, et al. Neurochemical effects of olanzapine in first-hospitalization manic adolescents: a proton magnetic resonance spectroscopy study. Neuropsychopharmacology 2006;31:1264–1273
118. Perlis RH. Use of treatment guidelines in clinical decision making in bipolar disorder: a pilot survey of clinicians. Curr Med Res Opin 2007;23:467–475
119. Parker G, Tully L, Olley A, et al. The validity and utility of patients' daily ratings of mood and impairment in clinical trials of bipolar disorder. Acta Psychiatr Scand 2007;115:366–371
120. Rizvi S, Zaretsky AE. Psychotherapy through the phases of bipolar disorder: evidence for general efficacy and differential effects. J Clin Psychol 2007;63:491–506

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