*Key Words: bipolar disorder, mood stabilizers, atypical antipsychotics, bimodal treatment*

# Mood Stabilizers and Atypical Antipsychotics: Bimodal Treatments for Bipolar Disorder

*By Terence A. Ketter, MD, Henry A. Nasrallah, MD, and Andrea Fagiolini, MD*

***ABSTRACT*** *~ Treatment options for bipolar disorder have rapidly expanded over the last decade, but providing optimal management remains an elusive goal. The authors reviewed the literature on the efficacy of agents with the best clinical evidence supporting their use in bipolar disorder, including the mood stabilizers lithium, valproate, lamotrigine, and carbamazepine, as well as the atypical antipsychotics olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole. Most medications appear to be more effective for symptoms of mood elevation than for symptoms of depression. The efficacy, tolerability, and safety profiles of agents must be considered when making clinical decisions. Several agents, including lithium, valproate, olanzapine, quetiapine, and risperidone, can cause problematic weight gain. In addition, the use of atypical antipsychotics has been associated with an increased risk of metabolic abnormalities such as dyslipidemia, hypergylycemia, and diabetes mellitus. In most patients, monotherapy offers inadequate efficacy. Further investigation of combinations of agents such as mood stabilizers and atypical antipsychotics may yield valuable insights into the potential of combination therapies to enhance clinical outcomes in patients with bipolar disorder.* Psychopharmacology Bulletin. *2006;39(1):120–146.*

## INTRODUCTION

Bipolar disorder, formerly known as manic depressive illness, is a disease characterized by dramatic mood swings, between abnormal euphoria, expansiveness, or irritability (during manic or hypomanic episodes), and pervasive sadness and anhedonia (in depressive episodes), often with interspersed periods of subsyndromal symptoms as well as times with normal mood.[1]

Current estimates of the lifetime prevalence of bipolar spectrum disorders range from 3% to 6.5% of the population.[2,3] Although bipolar illness can develop at different ages, the peak period of onset appears to be during late adolescence or early

Dr. Ketter is at the Stanford University School of Medicine, Stanford, CA; Dr. Nasrallah is at the University of Cincinnati Medical Center, Cincinnati, OH; Dr. Fagiolini is at the University of Pittsburgh Medical Center, Pittsburgh, PA.

To whom correspondence should be addressed: Terence A. Ketter, Stanford University School of Medicine, 401 Quarry Road, Room 2124, Stanford, CA 94305; Tel: 650-723-2515; Fax: 650-723-2507; E-mail: tketter@stanford.edu

adulthood.[4] Common presentations include major depressive episodes, and in children and adolescents, atypical affective disorders with more continuous and mixed symptoms as well as disruptive behavior disorders such as attention-deficit/hyperactivity disorder.[5-7] Patients commonly have concurrent difficulties with other psychiatric conditions such as alcohol and substance abuse, anxiety disorders, eating disorders, and Cluster B personality traits/disorders. Thus, early diagnosis presents a substantial challenge, and a decade commonly passes between first symptoms and appropriate diagnosis and treatment.[8]

As described in the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, Text Revision (*DSM-IV-TR*),[1] primary bipolar disorders are divided into 4 categories: bipolar I disorder, bipolar II disorder, cyclothymic disorder, and bipolar disorder not otherwise specified (NOS). Bipolar I disorder is characterized by a history of 1 or more manic or mixed episodes, usually accompanied by 1 or more major depressive episodes. Bipolar II disorder is characterized by a history of recurrent major depressive episodes, with 1 or more hypomanic episodes, and the absence of manic and mixed episodes. Cyclothymic disorder is characterized by a chronic pattern of numerous periods of mood elevation and depressive symptoms that do not meet the criteria for manias, hypomanias, or major depressive episodes. Bipolar NOS includes disorder with bipolar features that do not meet the criteria for any specific bipolar disorder.[9]



This complex and devastating illness is associated with a significant social and economic burden. There is a high risk of suicide attempts, and studies in bipolar patients indicate that 25% to 50% have attempted suicide at least once. In addition, it is suggested that up to 19% of patients with bipolar disorder die from suicide.[10] The disease can also cause significant psychosocial morbidity that may affect multiple aspects of patients' lives, including relationships with family members/caregivers and employment.[11,12] Each year in the United States alone, about 100,000 people will have an initial acute episode of bipolar disorder. Thus, bipolar disorder results in significant human and economic burdens. Based on incidence data and the projected course of illness, the total lifetime cost of people with onset of bipolar disorder in 1998 was estimated at $24 billion (US).[13]

### *Limitations of Current Treatment Options*

All too often, treatment fails to provide comprehensive control of bipolar illness. Some agents offer only unimodal relief of symptoms. For example, traditional antipsychotics are effective for mania, but can exacerbate depression, while antidepressants can relieve depression, but risk

provoking switches into mania.[14] Mood stabilizers (such as lithium, valproate, lamotrigine, and carbamazepine) and atypical antipsychotics may offer more bimodal symptomatic relief. But, with the exception of lamotrigine, these agents tend to be more effective for the mood elevation than for the depressive aspects of bipolar disorder.[15] The longitudinal course of bipolar disorders is chronic.[16] Symptom severity fluctuates frequently within the same patient over time, involving most often subsyndromal and minor affective depressive symptoms.[17,18] Poor response occurs in approximately 35% of patients, while the significant side effects associated with many agents used to treat this disorder can undermine compliance. Currently, there are a variety of available treatment options for those with bipolar disorder, including somatic and adjunctive psychosocial treatments.

### *Somatic Treatments*

**Pharmacologic Therapies.** There are several agents currently available for the treatment of bipolar disorder. The initial treatment of bipolar disorder depends on the type of episode the patient is experiencing at presentation. The United States Food and Drug Administration (FDA)-approved medications for 1 or more phases of bipolar disorder include mood stabilizers (lithium, valproate, lamotrigine, and extended-release carbamazepine), antipsychotics (chlorpromazine, olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole), and the combination of olanzapine/fluoxetine for depression associated with bipolar I disorder.[19-29]



### *Limitations of Currently Available Bipolar Therapies*

Although the number of pharmacologic treatment options available for the management of bipolar disorder has rapidly expanded over the last decade, providing optimal treatment remains an elusive goal.[30] Two areas of clinical concern are the poor response rates observed in approximately 35% of treated patients (particularly with respect to control of depressive symptoms) and the significant side effects associated with several of the currently available bipolar therapies, which can lead to patient noncompliance.

### *Background of the Term "Mood Stabilizer"*

Although the term "mood stabilizer" is not recognized by the FDA, it is a clinical term commonly used in the psychiatric literature that has gained wide acceptance. However, an expert consensus definition for the term has yet to be established. At present, there are several approaches to defining a mood stabilizer, some liberal and others conservative. In a more liberal approach, a mood stabilizer can be defined as an agent with

efficacy in 1 or more phases of bipolar disorder (acute mania, acute depression, or prophylaxis of mania and depression) that does not worsen acute episodes or increase an affective switch to the opposite mood state.[31,32] In a more conservative approach, a mood stabilizer can be defined as an agent that has both antidepressant and antimanic properties.[33] Ghaemi[14] has suggested a definition of demonstrable efficacy in 2 of 3 areas (acute mania, acute depression, and prophylaxis of mania and/or depression). Alternatively, bipolar illness can be viewed as including aberrations of affect from baseline (euthymia), and mood stabilizers as agents that stabilize mood from "above baseline" (by attenuating mania, mixed states, hypomania, and subsyndromal mood elevation) and/or "below baseline" (by attenuating depression and subsyndromal depression).[15] The difficulty reaching a consensus has led some to suggest that the term "mood stabilizer" should be abandoned.[34] Nevertheless, the term "mood stabilizer" is commonly used in clinical parlance to conveniently refer collectively to nonantipsychotic agents approved for the treatment of bipolar disorder (lithium, valproate, lamotrigine, and extended-release carbamazepine), and in this article we will use this "common usage" definition.



As proposed by Calabrese and Rapport,[33] the ideal mood stabilizer would equally effectively treat both acute mania and depression as well as provide prophylaxis over the long term. Unfortunately, such a balanced agent does not currently exist. Even lithium, the classical therapy for bipolar disorder, is not ideal. Lithium treatment is associated with safety and tolerability limitations as well as a treatment failure rate of up to 50%, and provides suboptimal responses in several subtypes of bipolar disorder.[35-39] In many instances, patients must receive combination therapy to achieve adequate control of their illness.

To date, we do not have adequate understanding of the mechanisms of action of mood stabilizers, nor have we identified a specific pathophysiologic abnormality in bipolar disorder.[40] Much of what is currently hypothesized is based upon as-yet unproven theories regarding the molecular mechanisms of the disease that have been extrapolated from the putative mechanisms of the various agents. Given the complexity of bipolar disorder and the numerous effects of mood stabilizers, there remains much left to understand.

Nevertheless, there are some theories about drug mechanisms and the pathophysiology of bipolar disorder that appear to be credible in the light of available evidence. Because antidepressants and some mood stabilizers (such as lithium and lamotrigine)[14,39] take more than a week to begin to exert their clinical effects and do not achieve full efficacy until several weeks have passed, it is reasonable to hypothesize that their primary

effect is not exercised through direct receptor actions.[41] Alterations in postreceptor pathways, intracellular signaling, neural plasticity, and changes in gene expression may play important roles in the therapeutic effects of these compounds. Indeed, clinical and preclinical evidence suggests that alterations in second messenger systems and G proteins may contribute importantly to the pathophysiology of bipolar disorder.[41]

## MOOD STABILIZERS AND ATYPICAL ANTIPSYCHOTICS

Below we review in more detail agents that appear to have the best evidence supporting their use in the treatment of bipolar disorder, namely, the mood stabilizers lithium, valproate, lamotrigine, and carbamazepine, and the atypical antipsychotics olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole. In addition, we discuss the combination of olanzapine plus fluoxetine. Table 1 summarizes efficacy associated with mood stabilizers and atypical antipsychotics.

### *Lithium*



Lithium is the best studied of the mood stabilizers, and the evidence for its efficacy is compelling. The risk of occurrence of a manic,

**TABLE 1**

**EVIDENCE FOR MOOD STABILIZERS AND ATYPICAL ANTIPSYCHOTICS AS TREATMENT OPTIONS IN BIPOLAR DISORDER**

| AGENT | PHASES OF BIPOLAR DISORDER | | | |
|---|---|---|---|---|
| | *Mania* | *Mixed* | *Maintenance* | *Bipolar I Depression* |
| Lithium | A[44,90,117] | — | A[45,47,48] | +[42] |
| Valproate | A[44,54,118] | +[44] | +[60,119] | — |
| Lamotrigine | — | — | A[47,48] | +[67] |
| Carbamazepine extended-release capsules | A[72,73] | A[72,73] | +[36,37,45,76] | — |
| Olanzapine | A[56,57,80,81] | A[56,57,80,81] | A[78,79] | +[83] |
| Risperidone | A[86,120] | A[121] | — | — |
| Quetiapine | A[89,90] | — | — | +[93] |
| Ziprasidone | A[94] | A[94] | — | — |
| Aripiprazole | A[96,97] | A[96,97] | A[98] | — |
| Olanzapine/ fluoxetine HCl* | — | — | — | A[83] |

*Combination treatment in one formulation
A = U.S. Food and Drug Administration (FDA) approved
+ = Clinical evidence of efficacy (not FDA approved)
— = Little or no clinical evidence of efficacy to date (not FDA approved)

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hypomanic, or depressive episode was 3.6-fold greater with placebo compared with lithium therapy in 11 placebo-controlled, parallel-group studies.[42] Other data indicate that up to 2/3 of acutely manic patients experience at least some improvement with lithium therapy.[39] Importantly, lithium may reduce the rate of suicide among bipolar patients.[42] Clinical studies have also compared the efficacy of lithium with that of other agents in the treatment of acute mania. In a double-blind study, 179 hospitalized, acutely manic patients were randomized to treatment with lithium, valproate, or placebo for up to 3 weeks. The percentages of patients improving at least 50% on the Schedule for Affective Disorders and Schizophrenia Mania Rating Scale were comparable for lithium (49%; $P = .025$) and valproate (48%; $P = .004$) and superior to placebo (25%).[43] Similar findings were reported in another 3-week study in which both lithium and valproate produced significant and comparable improvement in manic symptoms.[44]

Lithium also has been found to be efficacious in bipolar maintenance.[45] A meta-analysis of 19 blinded, randomized, prophylaxis trials of lithium versus placebo in 865 patients with either bipolar or unipolar affective disorders found 74% of patients had a recurrence on placebo versus 29% of patients taking lithium. This difference in relapse rate was highly significant.[45] The prophylactic efficacy of lithium has also been evaluated in comparative trials with other agents. A meta-analysis of the results from 10 studies of lithium versus carbamazepine reported that these agents had comparable efficacy.[45] In a recent, randomized, double-blind trial, the efficacy of lithium was compared with that of valproate over a 52-week maintenance period in 372 outpatients with bipolar I disorder. Perhaps due to methodologic limitations, the results indicated no greater efficacy for lithium than for valproate or placebo on the primary outcome measure of preventing recurrence of either a manic or depressive mood episode.[46] However, benefits with active treatments compared to placebo were evident on some secondary outcome measures in several post hoc analyses. Another recent clinical trial compared lithium with lamotrigine as maintenance therapy in recently manic or hypomanic patients (n = 175) with bipolar I disorder, and found that lamotrigine was as effective as lithium, and both were more effective than placebo at prolonging the time to intervention for any emergent mood episode (mood elevation or depression).[47] However, only lithium was superior to placebo at prolonging time to intervention for a manic, hypomanic, or mixed episode (lithium vs. placebo, $P = .006$; lamotrigine vs. placebo, $P = .28$), while only lamotrigine was superior to placebo at prolonging time to intervention for a depressive episode (lamotrigine vs. placebo, $P = .02$; lithium vs. placebo, $P = .17$).[47] A

similar study in recently depressed patients had a similar pattern of findings.[48] In a subsequent pooled analysis of these studies, a modest mania prevention effect was noted for lamotrigine.[49] Taken together, these data are consistent with the notion that lithium may "stabilize mood from above baseline" while lamotrigine may "stabilize mood from below baseline."[15]

When considered specifically for its effect on bipolar depression, evidence suggests that lithium maintenance therapy may benefit a significant number of patients with bipolar depression.[15] However, dropout rates in clinical trials of lithium maintenance therapy are high, and a significant number of patients have suboptimal responses, emphasizing the need for other treatment options for bipolar depression. Also, data suggest that lithium works well in bipolar disorder patients with the classical form of the illness, but may be less effective in those with other presentations such as mixed states and rapid cycling.

Although lithium has been used to treat bipolar disorder for over 50 years, there are some distinct limitations with this compound. First, lithium therapy may fail to provide prophylactic efficacy in up to 50% of treated patients.[50] In addition, it has a narrow therapeutic index, and patients taking this medication must comply with blood level monitoring, as severe toxic effects can occur at only twice the therapeutic dose.[40,42] This limitation is particularly important in patients with any kind of renal impairment, which increases blood levels of the drug.[40] Additional adverse effects that occur with lithium include polyuria, polydipsia, gastrointestinal (GI) effects, thyroid dysfunction, and weight gain.[42,51,52] In view of the possibility of abrupt lithium withdrawal increasing the risk of relapse, it is recommended that patients be gradually tapered off lithium.[45]



### *Valproate*

Research into the use of anticonvulsants, including valproate, for the effective treatment of mania began in the 1970s. Valproate was found to be superior to placebo and associated with significant improvement (at least a partial response or >50% reduction in manic symptoms) in 54% of patients treated for acute mania in pooled data from 3 parallel-designed, double-blind, controlled studies.[38,44,53,54] Furthermore, in a study of patients suffering from acute mania with psychotic symptoms, valproate was found to be rapidly effective and adequately tolerated in some patients.[38] Patients with rapid cycling, mixed mania, and mania with comorbid substance abuse may respond better to valproate than to lithium—a significant consideration because these features are evident in a large percentage of bipolar patients.[38,42]

In a large meta-analysis of comparative trials of valproate versus lithium for treatment of acute mania, no significant differences were found between the 2 agents as measured by changes on the Clinical Global Impression—Improvement (CGI-I) or the Young Mania Rating Scale (YMRS).[55] Similarly, in trials of valproate versus carbamazepine, there was no significant difference in the number of patients who failed to respond clinically between the 2 medications.[55] In 2 acute mania studies of valproate versus olanzapine, olanzapine tended to be somewhat more effective but somewhat more poorly tolerated, due to sedation and weight gain.[56,57] Thus, both efficacy and the side effect profiles of these agents need to be considered carefully in clinical decision making.

The implications of long-term therapy with valproate were recently examined in a double-blind, parallel-group study conducted over a 52-week period in 372 bipolar patients recently recovered from a manic episode and randomized within 3 months of that episode to maintenance therapy with valproate, lithium, or placebo in a 2:1:1 ratio.[58] Perhaps due to methodologic limitations, time to recurrence of any mood episode (the primary outcome measure) did not differ significantly among the groups. However, valproate appeared effective on some secondary outcome measures, and thus was more effective than either lithium or placebo at preventing the recurrence of an affective episode severe enough to cause withdrawal from the study.[59] Additional analyses from that study evaluated the maintenance efficacy of valproate, lithium, or placebo for prevention of bipolar depression. It was found that valproate-treated patients had less worsening of depressive symptoms than lithium-treated patients, especially among patients who had responded to valproate when manic during the open stabilization phase prior to randomized double-blind treatment and those with a more severe prior course of illness.[60]

Valproate, like lithium, requires medical monitoring and can yield clinically significant adverse effects.[42] Common side effects include sedation, ataxia, lethargy, dizziness, infection, tinnitus, weight gain, hematologic dysfunction, and alopecia.[42,55] Hepatotoxicity, pancreatitis, and teratogenicity are serious complications that have been associated with valproate therapy. Emerging data suggest that in epilepsy patients and bipolar disorder patients, the use of valproate may be associated with polycystic ovarian syndrome.[61,62] Also, in epilepsy patients, valproate may yield significant reductions in axial and appendicular bone mineral density.[63,64] During pregnancy, the use of valproate confers a substantial increase in the risk of major complications or other significant pregnancy complications, and the incidence of major congenital malformations may be as high as 11%.[65] The teratogenic effects

associated with valproate use during pregnancy include neural tube defects, congenital heart lesions, digital anomalies, oral clefts, and craniofacial dysmorphic features.

Comparisons of valproate with lithium suggest that valproate may have a more favorable overall side effect burden,[43,46] although individual patients may tolerate 1 agent better than the other.[42] In recent studies comparing valproate with olanzapine in the treatment of acute mania, olanzapine was modestly more effective, but valproate had some safety and tolerability advantages.[56,57,66] Valproate appeared to decrease both serum total cholesterol and low-density lipoprotein cholesterol (LDL-C) levels slightly, while olanzapine increased both values. There was a significant treatment difference noted for platelet counts, with valproate-treated patients showing a decreased platelet count from baseline levels. Weight gain occurred with both medications, but was more evident with olanzapine. Nevertheless, in the valproate group, 20% of patients gained from 5 to 10 lb, and another 20% gained more than 10 lb over the course of the 12-week study.



### *Lamotrigine*

Lamotrigine appears effective in treating depressive aspects of bipolar disorder. In 1 double-blind study, 195 outpatients with bipolar I disorder experiencing a major depressive episode were randomized to lamotrigine 50 mg/day (n = 66), lamotrigine 200 mg/day (n = 63), or placebo (n = 66) as monotherapy for 7 weeks.[67] Lamotrigine at the 200-mg/day dose demonstrated antidepressant efficacy, and over 50% of this treatment group met response criteria on the Hamilton Depression Rating Scale (HDRS), Montgomery-Asberg Depression Rating Scale (MADRS), and CGI-I scales. For the MADRS, this rate of improvement was significantly higher and nearly twice that observed with placebo. Efficacy with the lamotrigine 50-mg/day dose was noted on fewer measures, and the percentage of responders was lower. Use of lamotrigine did not appear to provoke switches to mania, with the frequency of manic, hypomanic, or mixed episodes being similar in both active medication and placebo groups.[67]

Two maintenance trials found lamotrigine effective for delaying time to intervention for any emergent mood episode (depression or mood elevation), and particularly for delaying time to intervention for emergent depressive episodes. In 1 of these double-blind, placebo-controlled trials, 175 recently manic or hypomanic patients with bipolar I disorder were randomized to lamotrigine (n = 59), lithium (n = 46), or placebo (n = 70) for up to 18 months.[47] Lamotrigine and lithium demonstrated equal efficacy and superiority to placebo in delaying time to intervention for

any mood episode. Yet although lamotrigine monotherapy was found to be superior to placebo in prolonging the time to intervention for emergent depressive episodes, it did not achieve statistical superiority to placebo at prolonging time to intervention for manic, hypomanic, or mixed episodes. However, there was no evidence that manic symptoms worsened with lamotrigine.[47] As noted above, a similar study in recently depressed patients had a similar pattern of findings.[48] Taken together, the available data suggest that lamotrigine has its most robust efficacy in preventing recurrence of depressive symptoms, with only modest efficacy in preventing mania. In addition, controlled studies suggest that lamotrigine is not effective in the treatment of acute mania in patients with bipolar disorder.

Lamotrigine was generally well tolerated in clinical trials, and may be better tolerated than lithium in maintenance therapy.[49] The most common adverse event reported with the use of lamotrigine was a headache. A rash appeared to lead to discontinuation of lamotrigine in approximately 5% to 6% of patients taking the drug, but the possibility of this result may be decreased with careful dose titration.[67] Far less common is serious rash, which may be seen in 0.02% to 0.1% of patients.[68]



### *Carbamazepine*

Carbamazepine has been used for over 3 decades to treat bipolar illness. It has been employed as monotherapy and as adjunctive medication in the treatment of acute mania and for the prophylaxis of both mania and bipolar depression.[40,69,70] In head-to-head comparison studies with lithium, chlorpromazine, and haloperidol in the treatment of acute mania, carbamazepine has been associated with improvement over baseline and found to be as efficacious as these comparator agents.[69]

Early trials of carbamazepine in bipolar disorder were conducted with a standard immediate-release formulation. New extended-release formulations of carbamazepine provide less variation in plasma concentrations and less variable absorption, which may result in better central nervous system tolerability than is achieved with immediate-release formulations.[71] Recently, carbamazepine extended-release capsules (CBZ-ERC; 200–1600 mg/day) have been investigated as monotherapy in 2 similar randomized, multicenter, double-blind, placebo-controlled trials in patients with manic or mixed episodes associated with bipolar I disorder;[72,73] the data were also combined for additional analysis. The trials randomized 443 patients to double-blind treatment—223 to CBZ-ERC and 220 to placebo—240 of whom completed the 21-day study period.[74] The discontinuation rate was higher in the placebo group due to lack of efficacy. By the end of the trial, 52% of

CBZ-ERC–treated patients had responded (achieved a ≥50% decrease in YMRS score) versus 26% of those treated with placebo ($P < .0001$). Subgroup analysis suggested that carbamazepine was effective for treatment of both pure manic and mixed episodes. Patients on carbamazepine also experienced significantly greater improvement on the CGI-I and Clinical Global Impression—Severity scales than did patients in the placebo group ($P < .0001$).[74] Additionally, there was a significant improvement in HDRS scores in the active treatment group ($P < .05$). The reduction in depressive symptoms with CBZ-ERC therapy is of clinical interest, as it is consistent with the possibility that carbamazepine may have antidepressant effects in bipolar disorder, in agreement with prior observations.[75]

In an open-label extension trial, patients who had completed 1 of the 2 21-day trials (as well as those from a sister study of patients unresponsive to lithium) received 6 months of CBZ-ERC therapy.[35] Of the 92 patients enrolled, 67% had mixed episodes and 33% had manic episodes; 24 patients (31.2%) completed the study. The relapse rate during the study period was 14.3%, a figure that compares favorably with relapse rates reported for lithium therapy. Patients who had previously been treated with placebo experienced a 60% reduction in YMRS scores in the first month of active therapy. Even patients who had received prior active therapy showed a trend toward further improvement in YMRS scores.



Carbamazepine has been evaluated as maintenance therapy in at least 10 double-blind, randomized clinical trials, and response rates have ranged from 30% to 60%.[50] Several studies have compared carbamazepine with lithium and have most often shown overall response rates to be comparable in the prevention of recurrent bipolar episodes. A meta-analysis of 10 blinded, randomized, comparative trials of lithium versus carbamazepine, conducted in 572 patients over a period of 1 to 3 years, found 60% of patients had a recurrence on lithium versus 55% of patients on carbamazepine; the difference in relapse rates between the 2 treatment groups was not statistically significant.[45] One study found carbamazepine to have efficacy and tolerability equal to lithium in prophylaxis of bipolar disorder among patients not selected for lithium resistance, indicating that positive results for carbamazepine were not merely the result of selection bias.[76] In another study comparing carbamazepine therapy with lithium in the prophylaxis of bipolar disorder, lithium appeared to be more beneficial in patients with classical bipolar I disorder (without mood-incongruent delusions, without comorbidity, and without mixed states), and carbamazepine tended to be more effective in the nonclassical subgroup,[37] giving support to the theory that some mood stabilizers may be more effective in certain subgroups of patients.[77]

Carbamazepine has been generally well tolerated in clinical trials,[72,73] especially if introduced gradually.[35] The most common adverse events reported with carbamazepine have included dizziness, nausea, somnolence, vomiting, dyspepsia, and dry mouth.[72,73] Up to 10% of patients may experience benign rash or benign leukopenia, while only about 1 in 100,000 may experience serious hematologic or dermatologic adverse effects. In longer term therapy carbamazepine appears to have a low propensity towards weight gain.[35] Carbamazepine has clinically significant drug interactions, as it can induce metabolism of multiple psychotropic (including valproate, lamotrigine, and several atypical antipsychotics, antidepressants, and anxiolytics) and general medical (including several anticonvulsants, analgesics, antibiotics, steroids, and muscle relaxant) drugs, potentially compromising the efficacy of these agents. In addition, other drugs (such as cytochrome P450 3A4 inhibitors) can inhibit carbamazepine metabolism, potentially yielding carbamazepine toxicity.

*Olanzapine*



Olanzapine, an atypical antipsychotic, was approved by the FDA in 2000 for the treatment of acute manic and mixed episodes associated with bipolar disorder and, more recently, as maintenance therapy for bipolar disorder.[78,79] Olanzapine has been shown to be superior to placebo[80,81] in the treatment of acute manic and mixed episodes. In 2 3-week, double-blind, randomized studies of olanzapine versus placebo in patients with bipolar disorder, olanzapine-treated patients demonstrated significantly greater improvements on the YMRS total score than placebo patients. In 1 of these studies (n = 139), 49% of olanzapine-treated patients experienced a response (≥50% improvement in mean YMRS score) compared with 24% of placebo-treated patients ($P < .01$).[80] In the second study (n = 115), 65% of olanzapine-treated patients responded compared with 43% of placebo-treated patients ($P < .01$).[81] Subgroup analysis of the results of these trials suggested that olanzapine is effective for treatment of acute mania, both mixed and pure manic, independent of the presence or absence of psychosis.

In a pooled analysis of 2 6-week, multicenter, randomized, double-blind, placebo-controlled acute mania studies, olanzapine or placebo was added in patients with inadequate responses to at least 2 weeks of lithium (mean serum concentration, 0.76 mEq/L) or valproate (mean serum concentration, 64 μg/mL) monotherapy.[82] The YMRS response rate was greater in 220 patients on combination therapy (68%) than in 114 patients on mood stabilizer monotherapy (45%; $P < .001$), and the mean time to response was shorter with olanzapine plus mood stabilizer (18 days) than with

mood stabilizer monotherapy (28 days; $P = .002$). Combination treatment compared to monotherapy yielded more somnolence, dry mouth, tremor, slurred speech, increased appetite, weight gain, and significantly more discontinuations due to adverse events (10.9% vs. 1.7%; $P = .002$).

The efficacy of olanzapine in acute mania has also been evaluated in comparative studies with valproate. In 1 3-week, double-blind, randomized, controlled, comparative trial of hospitalized patients with acute manic or mixed episodes associated with bipolar disorder (n = 148), olanzapine was found to be superior to valproate, which was started at a modest initiation dose of 750 mg/day. At endpoint, 54% of olanzapine-treated patients responded (≥50% reduction in YMRS) compared with 42% of valproate-treated patients.[56] In a separate study to assess the efficacy of olanzapine in comparison with valproate, investigators found no significant differences between the 2 agents in the efficacy of treatment for acute mania (although olanzapine tended to be more effective), nor any differences for individuals displaying psychotic symptoms.[57] The trial, conducted over a 12-week period in patients hospitalized with acute mania (n = 120), used valproate loading at 20 mg/kg, an initiation strategy more in keeping with current clinical practice than those used in the previous study. Sample size limitations may have accounted for the lack of separation of efficacy between valproate and olanzapine in this study. Taken together, these 2 acute mania studies suggest that, compared with valproate, olanzapine tended to be somewhat more effective, but somewhat more poorly tolerated, due to sedation and weight gain.



In addition to its proven efficacy in acute mania, the use of olanzapine has been evaluated in combination with the antidepressant fluoxetine in treatment strategies for bipolar depression. One recent large, double-blind, randomized, placebo-controlled trial compared olanzapine alone and in combination with fluoxetine in the treatment of bipolar I depression.[83] The 8-week study found that patients treated with olanzapine (n = 351) showed significant improvement in depressive symptoms as measured by the MADRS compared with placebo (n = 355) starting at week 1 of acute therapy ($P < .001$). The study also found that the combination of olanzapine with fluoxetine (n = 82) was significantly superior in all efficacy measures of depression compared not only with placebo but also compared with olanzapine monotherapy. As for the possibility of treatment-emergent mania, the study found no increased risk of developing manic symptoms when fluoxetine was added to olanzapine therapy. The combination olanzapine/fluoxetine is currently (as of mid-2005) the only FDA-approved treatment for acute bipolar I depression.

Additionally, olanzapine has shown efficacy in bipolar maintenance therapy. Multicenter, randomized, double-blind, placebo-controlled trials

indicate that olanzapine as maintenance monotherapy for bipolar disorders after acute manic episodes was superior to placebo[78] and comparable (and on some measures superior) to lithium.[79] In the above studies, olanzapine tended robustly to prevent mania and more modestly to prevent depression. Mean olanzapine doses in these monotherapy maintenance trials after acute manic episodes were approximately 12 to 16 mg/day, and sedation and weight gain were the main adverse effects. There are only limited data regarding the efficacy of olanzapine as continuation and maintenance therapy after acute depressive episodes in bipolar disorders. In a 52-week continuation study, approximately 3/4 of patients who remitted in an 8-week acute depression study who were placed on open olanzapine monotherapy required addition of open fluoxetine, and even with this intervention allowed, about 45% relapsed (primarily into depression).[84]

Olanzapine therapy has been associated with significant weight gain. In a comparative study with valproate, 23% of olanzapine-treated patients gained 5 to 10 lb, and another 35% gained more than 10 lb over 12 weeks of treatment. Mean increase from baseline body weight at final evaluation was 8.8 lb in the olanzapine group versus 5.5 lb in the valproate group ($P = .049$).[57] Olanzapine was also associated with significant increases in serum total cholesterol and LDL cholesterol levels. The FDA has recently required changes in the olanzapine product labeling (and that of other atypical antipsychotics) to reflect the risk of hyperglycemia and diabetes mellitus. The report of a consensus development conference in November 2003 suggested the risks of obesity, diabetes, and hyperlipidemia with this agent (and with clozapine) were greater than those associated with other newer antipsychotics.[85] Thus, clinical and (as indicated) laboratory monitoring for obesity, diabetes, and hyperlipidemia appears prudent for patients receiving olanzapine.



### *Risperidone*

To date, several additional atypical antipsychotics, including risperidone, quetiapine, ziprasidone, and aripiprazole have received FDA approval as treatment options for bipolar disorder. Emerging data suggest that, like olanzapine, at least some of these agents may have utility for other aspects of bipolar disorder. Risperidone has been shown to be effective in the treatment of acute mania in 2 3-week, double-blind, placebo-controlled trials. In 1 study, 43% of risperidone-treated patients (n = 125) were considered responders (≥50% decrease in YMRS score) compared with 24% of placebo-treated patients (n = 134) at endpoint ($P < .001$). In this study, the efficacy of risperidone was established in patients with and without psychosis, and significant improvement was observed 3 days after treatment initiation.[86] A second study in

290 patients confirmed these results with a 73% response rate in the risperidone treatment group (n = 146) versus a 36% response rate in the placebo group (n = 144) ($P < .001$).[87]

In a 3-week, multicenter, randomized, double-blind, placebo-controlled acute mania study, risperidone, haloperidol, or placebo was combined with lithium or valproate.[88] Risperidone doses were 2 mg on days 1 and 2, 1 to 4 mg on days 3 and 4, and 1 to 6 mg/day thereafter, with a mean modal dose of 3.8 mg/day. Haloperidol doses were 4 mg on days 1 and 2, 2 to 8 mg on days 3 and 4, and 2 to 12 mg/day thereafter, with a mean modal dose of 6.2 mg/day. The YMRS response rate tended to be greater in 52 patients on risperidone plus mood stabilizer combination therapy (57%) and in 53 patients on haloperidol plus mood stabilizer combination therapy (58%) than in 51 patients on mood stabilizer monotherapy (38%). Compared to monotherapy, risperidone plus mood stabilizer combination treatment yielded more weight gain (+5.3 lb vs. +0.3 lb), and haloperidol plus mood stabilizer combination treatment yielded more extrapyramidal symptoms.



The most common risperidone adverse effects with monotherapy are somnolence, dystonia, akathisia, dyspepsia, nausea, parkinsonism, blurred vision, and increased salivation, and with adjunctive therapy are somnolence, dizziness, parkinsonism, increased salivation, akathisia, abdominal pain, and urinary incontinence. Risperidone also causes hyperprolactinemia, so that assessment of serum prolactin may prove useful in patients who present with menstrual irregularities, galactorrhea, and difficulties with sexual desire and function. The FDA has recently required changes in the risperidone product labeling to reflect the risks of hyperglycemia and diabetes mellitus. The report of a consensus development conference in November 2003 suggested the risks of obesity, diabetes, and hyperlipidemia with this agent were less than those associated with clozapine and olanzapine but greater than those associated with ziprasidone and aripiprazole.[85] Thus, clinical and (as indicated) laboratory monitoring for obesity, diabetes, and hyperlipidemia appears prudent for patients receiving risperidone.

### *Quetiapine*

In controlled monotherapy trials in acute mania (patients with mixed episodes were excluded), quetiapine yielded significantly greater mean YMRS decreases at weeks 3 and 12 compared with placebo. In 1 monotherapy study, at week 3, YMRS response rates for 102 patients on quetiapine (43%) and for 98 patients on haloperidol (56%) were significantly greater than in 100 patients on placebo (35%), with a similar finding at week 12 (quetiapine 61%, haloperidol 70%, placebo 39%).[89]

Quetiapine yielded significantly more weight gain and tended to cause more somnolence and postural hypotension compared with placebo. Haloperidol, when compared with placebo, significantly increased extrapyramidal symptoms, akathisia, and tremor. In another 12-week monotherapy study in acute mania, YMRS response rates at weeks 3 and 12 with quetiapine and lithium were similar and exceeded those of placebo.[90] The most common adverse events with quetiapine were dry mouth, somnolence, and weight gain.

In addition to its proven efficacy as monotherapy in acute mania, quetiapine has also been evaluated in combination with lithium or valproate. In a 3-week, multicenter, randomized double-blind, placebo-controlled trial in acute mania (patients with mixed episodes were excluded), the YMRS response rate of patients on quetiapine combined with lithium or valproate exceeded that of patients on either lithium or valproate monotherapy.[91] When compared with lithium or valproate monotherapy, combination therapy yielded more somnolence, dry mouth, asthenia, postural hypotension, and weight gain. In a pooled analysis of the above trial and a similar 6-week study, the YMRS response rate for patients on quetiapine plus mood stabilizer exceeded that of those on mood stabilizer monotherapy at week 3.[92] Quetiapine, in combination with lithium or valproate, yielded more somnolence, dry mouth, asthenia, postural hypotension, and weight gain than either lithium or valproate monotherapy.



Emerging data suggest that quetiapine may have utility in acute bipolar depression. Thus, in a recent 8-week, multicenter, randomized, double-blind, placebo-controlled trial, quetiapine administered at doses of 300 mg/day and 600 mg/day was effective in acute bipolar depression. Somnolence, dry mouth, and dizziness were the main adverse effects.[93]

The most common adverse events with quetiapine are somnolence, dizziness (postural hypotension), dry mouth, constipation, increased serum glutamate pyruvate transaminase, weight gain, and dyspepsia.[26] The FDA has recently required changes in the quetiapine product information to reflect the risks of hyperglycemia and diabetes mellitus. The report of a consensus development conference in November 2003 suggested the risks of obesity, diabetes, and hyperlipidemia with this agent were less than those associated with clozapine and olanzapine, but greater than those associated with ziprasidone and aripiprazole.[85] Thus, clinical and (as indicated) laboratory monitoring for obesity, diabetes, and hyperlipidemia appears prudent for patients receiving quetiapine.

### *Ziprasidone*

Ziprasidone has been shown to be effective in the treatment of acute manic and mixed episodes in 2 3-week, double-blind, placebo-controlled

trials. In 1 trial, 210 patients with bipolar I disorder and experiencing a manic or mixed episode were randomized in a 2:1 ratio to receive either ziprasidone (n = 140) or placebo (n = 70). At day 21, 50% of ziprasidone-treated patients were considered responders (≥50% decrease in YMRS score) compared with 35% of placebo-treated patients ($P < .05$).[94] Similar findings were observed in a second trial in which treatment with ziprasidone (n = 137) led to significant improvement compared with placebo (n = 65) on the YMRS. At day 21, 46% of ziprasidone-treated patients were considered responders (≥50% decrease in YMRS score) compared with 29% of placebo-treated patients ($P < .05$).[95]

The most common adverse events associated with discontinuation of ziprasidone in acute mania were akathisia, anxiety, depression, dizziness, dystonia, rash, and vomiting.[24] The most common adverse events with intramuscular ziprasidone in schizophrenia patients were headache, nausea, and somnolence.[24] The FDA has recently required changes in the ziprasidone product labeling to include the risks of hyperglycemia and diabetes mellitus. The report of a consensus development conference in November 2003 suggested the risks of obesity, diabetes, and hyperlipidemia with this agent were similar to those associated with aripiprazole and less than those associated with other newer antipsychotics.[85] Thus, clinical and (as indicated) laboratory monitoring for obesity, diabetes, and hyperlipidemia may be prudent for patients receiving ziprasidone. Ziprasidone is contraindicated in patients with a known history of QT prolongation or cardiac arrhythmias, recent acute myocardial infarction, or uncompensated heart failure, because of its dose-related prolongation of the QT interval and the possible connection of fatal arrhythmias with QT prolongation. Circumstances that may increase the risk of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval include bradycardia, hypokalemia, or hypomagnesemia, concomitant use of other drugs that prolong the QTc interval, and the presence of congenital prolongation of the QT interval.[24]



### *Aripiprazole*

Aripiprazole has been shown to be effective in the treatment of acute manic and mixed episodes in 2 3-week, double-blind, placebo-controlled trials. In 1 trial, 262 patients with bipolar I disorder experiencing an acute manic or mixed episode were randomized to receive aripiprazole (n = 130) or placebo (n = 132) over a 3-week study period. Response rates were significantly greater with aripiprazole than placebo at all time points and were evident by day 4. At endpoint (day 21), 40% of aripiprazole-treated patients were considered responders (≥50% decrease in YMRS score) compared with 19% of placebo-treated patients ($P < .005$).[96] In a

second 3-week trial, conducted in 272 acutely manic patients with bipolar I disorder, similar improvements in manic symptoms were observed during aripiprazole treatment (n = 137) compared with placebo (n = 135). At day 21, 53% of aripiprazole-treated patients were considered responders (≥50% decrease in YMRS score) compared with 32% of placebo-treated patients ($P < .01$).[97]

Aripiprazole was recently approved by the FDA as bipolar maintenance therapy. In a relapse prevention study, patients who had recently experienced a manic or mixed episode (n = 567) were enrolled in a stabilization phase receiving open-label aripiprazole for 6 to 18 weeks.[98] Those patients who met stabilization criteria (YMRS ≤ 10 and MADRS ≤ 13 for 4 consecutive visits or 6 weeks) were then entered into the 26-week, randomized, double-blind, placebo-controlled maintenance phase (n = 161). Time to relapse of symptoms was significantly prolonged with aripiprazole monotherapy compared with placebo ($P = .02$), and there was a significant reduction in the total number of relapses in patients treated with aripiprazole versus placebo (25% vs. 43%, respectively; $P = .013$).

Perhaps due to partial agonist effects at dopamine receptors, nausea and vomiting can occur in some patients if aripiprazole is started at the recommended dose for acute mania of 30 mg/day. Tolerability may be enhanced in patients with GI or other adverse effects if aripiprazole is initiated at 15 mg/day or lower for a few days before increasing to 30 mg/day. However, only 15% of patients who participated in the 2 double-blind trials mentioned above[96,97] required a reduction of the dose from 30 to 15 mg due to adverse effects, and an initial dose of 30 mg is often necessary when the medication is used as monotherapy for patients experiencing severe manic episodes. Akathisia, somnolence, and constipation may be encountered with aripiprazole, but weight gain is not generally a major concern.[23] The FDA has recently required that the aripiprazole product labeling include the risks of hyperglycemia and diabetes mellitus. The report of a consensus development conference in November 2003 suggested the risks of obesity, diabetes, and hyperlipidemia with this agent were similar to those associated with ziprasidone and less than those associated with other newer antipsychotics.[85] Thus, clinical and (as indicated) laboratory monitoring for obesity, diabetes, and hyperlipidemia may be prudent for patients receiving aripiprazole.



## OTHER AGENTS WITH MOOD-STABILIZING POTENTIAL

### *Anticonvulsants*

Given the success of the anticonvulsants carbamazepine, valproate, and lamotrigine in treating the mood swings of bipolar disorder, it is not

surprising that several new anticonvulsants have been investigated for use in this illness as well.

Gabapentin, which appears to have indirect GABAergic actions, has been used as either adjunctive or primary therapy for bipolar disorder in several studies. Unfortunately, gabapentin has failed to demonstrate therapeutic efficacy in the treatment of bipolar disorder in controlled studies. Thus, in a placebo-controlled trial of gabapentin as adjunctive treatment along with ongoing therapy with lithium and/or valproate in outpatients with acute mania or hypomania, gabapentin was found to be no better than adding placebo.[99] In addition, in a placebo-controlled study of lamotrigine and gabapentin monotherapy in treatment-resistant (mainly rapid-cycling bipolar) mood disorder inpatients, gabapentin monotherapy was no better than placebo.[100]

Topiramate is a newer anticonvulsant that has both GABAergic and antiglutamatergic actions.[101] In several trials topiramate proved no better or worse than placebo in adults with acute mania.[102] However, in a small 4-week, multicenter, randomized, double-blind, placebo-controlled, acute mania trial in adolescents, topiramate was found to be superior to placebo.[103] Thus, additional evaluation of topiramate in acute mania in adolescents may be warranted.



There have been anecdotal reports about successful use of the selective GABA reuptake inhibitor tiagabine in bipolar disorder, but open-label studies have raised safety concerns about combining this agent with other GABAergic medications and the potential for this compound to provoke absence seizures, especially during loading. Controlled studies are needed before anything definitive can be said about the usefulness of tiagabine in bipolar disorder.

Oxcarbazepine is a 10-keto derivative of carbamazepine, and limited data suggest that it might have acute antimanic effects. In a small, active-comparator 15-day acute mania study, patients treated with oxcarbazepine showed improvement comparable to that seen in patients on haloperidol. In a similar study, patients treated with oxcarbazepine showed improvement comparable to that in patients on lithium.[104] Compared with carbamazepine, oxcarbazepine has fewer drug interactions and appears to be better tolerated, perhaps because of the absence of an active epoxide metabolite. However, serious dermatologic reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported in association with oxcarbazepine use at a rate exceeding the background incidence rate in the general population by a factor of 3- to 10-fold.[105] Hyponatremia is observed in about 2.5% of patients, which may be more frequent than with carbamazepine. Also, the lack of difference between oxcarbazepine and lithium or haloperidol in the studies mentioned above

may have been influenced by the small sample sizes, which limited the statistical power. Clearly, larger controlled studies are necessary to evaluate the efficacy of oxcarbazepine in bipolar disorder.

*Electroconvulsive Therapy*

The most common indication for electroconvulsive therapy (ECT) is major depression. However, in a literature review that covered over 50 years' experience with ECT in the treatment of mania, it was found that ECT was associated with remission or marked clinical improvement in 80% of patients with manic episodes, including those whose manic episodes have responded poorly to pharmacotherapy.[106] In contrast, there are few data supporting the utility of ECT as maintenance therapy in patients with bipolar disorders. Further investigation of ECT use in bipolar patients has provided clinical evidence that ECT is associated with a substantial improvement in symptoms in treatment-resistant patients with mixed mania or bipolar depression. However, patients with mixed mania may exhibit a more rapid and marked response as well as a greater reduction in suicidal ideation. Whether bipolar depression is more or less responsive to ECT than unipolar major depression is an issue that should be explored in future studies.[107]



*Phototherapy*

Phototherapy with full-spectrum bright white lights (2,000 to 10,000 lux for 30 minutes to 2 hours per day) is a nonpharmacologic somatic treatment option for acute depressive symptoms in a small subgroup of patients with bipolar disorder characterized by a seasonal pattern. This subgroup experiences a greater number of depressive episodes in the fall or winter and hypomania or mania in the spring or summer. Phototherapy is generally well tolerated, but there have been reports of sleep disruption and switches into mania or hypomania. Because there are no large, well-controlled studies of phototherapy in patients with bipolar depression taking mood stabilizers, its use is considered empiric.[108] Also, there are few data supporting the utility of this intervention as maintenance therapy in patients with bipolar disorders.

*Adjunctive Psychosocial Treatments*

Although medications are essential during all phases of the illness, people with bipolar disorder are likely to benefit from adjunctive psychosocial interventions, including psychotherapy, to help achieve recovery from depressive episodes and maintain remission.[109,110] In contrast, there are few data supporting the utility of such interventions during mood elevation. Considerable clinical evidence indicates that

addition of psychosocial interventions to medications may significantly reduce depressive symptoms, enhance social adjustment and functioning, and reduce relapses and hospitalizations in bipolar patients. Psychosocial interventions for patients with bipolar disorder include psychoeducation, family therapy, group therapy, cognitive behavioral therapy, and interpersonal and social rhythm therapy.[111,112] Combining 1 or more of these psychosocial interventions with medication should be considered early in the course of illness to improve medication compliance and help patients identify prodromes of relapse, which may assist in preventing a recurrence. In addition, some interventions may have a beneficial effect on mood symptoms, particularly symptoms of depression, enabling patients to better manage their illness and interpersonal relationships.[113,114]

## CONCLUSIONS

Exceedingly well-tolerated treatments that are robustly efficacious in acute mania and acute depression, as well as in the maintenance treatment of bipolar disorder across its varied subtypes, would be ideal. Unfortunately, such agents have yet to be found. Nevertheless, the growing number of available treatments provides clinicians and patients important new options for management of bipolar disorder



In this review, we have examined the efficacy of the mood stabilizers lithium, valproate, lamotrigine, and carbamazepine, as well as the atypical antipsychotics olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole. These agents differ considerably from one another, and several factors must be considered when deciding upon a course of treatment for a particular patient. It is important to evaluate the overall efficacy and tolerability profile when choosing agents for the treatment of bipolar disorders. Bimodal medications—those that affect both manic and depressive symptoms—are the most desirable in this disorder. With the exceptions of lamotrigine and the combination of olanzapine plus fluoxetine, the currently available agents tend to be more effective for symptoms of mood elevation than for symptoms of depression.

Adverse event profiles are an important consideration in guiding clinical decisions and may affect compliance, an important issue in the management of bipolar disorder. Several of the available agents—lithium, valproate, olanzapine, quetiapine, and risperidone—can cause problematic weight gain. Among these, olanzapine appears to cause the greatest weight gain. The use of atypical antipsychotics has been associated with an increased risk of adverse metabolic outcomes, including weight gain, dyslipidemia, hyperlipidemia, insulin resistance resulting

in hyperglycemia, and the onset or exacerbation of diabetes.[115] In addition to these serious health risks, a recent study has shown that obesity is correlated with a poorer outcome in patients with bipolar I disorder. Obese patients were found to experience a greater number of lifetime depressive and manic episodes and present with more severe and difficult-to-treat affective episodes. They were also more likely to develop an affective recurrence, particularly a depressive recurrence.[116] In cases in which weight gain is clearly related to a specific medication, 1 option is switching to another agent or decreasing the dose, which may be a difficult decision if the medication has been effective at ameliorating symptoms.

Serious but uncommon adverse events are also a concern. Valproate has been associated with pancreatitis, polycystic ovaries, teratogenicity concerns, and may have effects on bone mineral density. Both carbamazepine and lamotrigine have been associated with common benign and rare serious rash, although the occurrence of the latter may be higher in patients taking lamotrigine. Carbamazepine has been associated with rare serious hematologic abnormalities. The extended-release formulations of certain agents may reduce the likelihood or severity of less serious side effects such as somnolence or dizziness. Moreover, combination therapy may not only reduce the necessary doses of individual agents and hence their side effects, but may also provide synergistic benefits to increase therapeutic effects. Ultimately, it remains crucial to individualize assessment of risk-benefit ratios for patients.



The medications described above have helped to enhance the management of bipolar disorder for many patients. Although they have significant limitations, these treatments offer hope of relief of the devastating symptoms of bipolar disorder. Further investigation of combinations of mood stabilizers and atypical antipsychotics for different subtypes of bipolar disorder should provide additional valuable treatment options. Some clinical trials conducted in bipolar disorder have been hindered by the difficulty of enrolling patients who are severely ill.[33] This limitation can make it a challenge to detect differences between active medication and placebo, because placebo rates can be higher in less impaired patients.[33] It is hoped that rigorous trials in patient populations that reflect the full spectrum of this disease will yield more definitive answers in the future. ✤

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