

Rationale for Using Lithium in Combination With Other Mood Stabilizers in the Management of Bipolar Disorder

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Bipolar disorder is a complex illness, and no single agent has been proven in randomized, placebo-controlled trials to effectively prevent and/or control all aspects of the illness—acute mania, rapid cycling, and breakthrough depression. However, for the most important issue, prophylaxis of episodes, lithium has more evidence of efficacy than any other agent. Like lithium, typical antipsychotics, carbamazepine, divalproex, and the atypical antipsychotic olanzapine are effective in the treatment of mania. Carbamazepine, divalproex, and olanzapine seem effective in preventing manic episodes but, like lithium, are less effective in preventing depression. Few trials have been conducted in the more difficult-to-treat characteristics of bipolar disorder, specifically, rapid cycling and breakthrough depression. For patients with rapid cycling, carbamazepine or divalproex therapy may improve symptoms, but only lamotrigine has been shown to reduce cycling, mostly in the bipolar II group, in a randomized, placebo-controlled study. For the treatment of depressive episodes, lithium and olanzapine have shown modest efficacy in controlled trials, and among the mood stabilizers, lamotrigine has the most robust effect. Because manic symptoms may respond best to one agent and depressive symptoms to another, combination therapy may be the optimal treatment for many patients with bipolar disorder. For example, lithium augmentation may improve overall response rates to treatment with carbamazepine or divalproex, and the lithium-lamotrigine combination should provide effective prevention of both mania and depression. Also, each mood stabilizer may be given at lower doses when given in combination, resulting in a reduced side effect burden and improved compliance.

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Because bipolar disorder is a complex illness with characteristics and a course that vary from patient to patient, there is no single treatment or combination of treatments that will work for all patients. However, there are several general principles that can improve the management of bipolar disorder (Table 1).

Before deciding what treatment will be best for a patient, the physician and patient can create a life chart, which is a sort of timeline that visually depicts the beginning and end of each episode, the timing of different treatments, and major life events. In the long run, a life chart is easier to construct than a traditional narrative history and provides a clearer picture of the natural course of illness and the impact of different treatments.

Physicians who treat bipolar disorder also need to address coexisting conditions such as substance abuse and, of course, the ultimate worst outcome of the disease, suicide. According to the Epidemiologic Catchment Area Study,¹ around 60% of patients with bipolar disorder meet lifetime criteria for substance use disorders, and alcohol or drug dependence account for around two thirds of these comorbid substance use disorders. Abused substances worsen the course of illness, negatively interact with medication, and decrease patients' medication compliance. Medication side effects represent another major reason for noncompliance, and the tragedy is that side effects often go undetected and/or untreated. The ultimate worst outcome of bipolar disorder is, of course, suicide, and estimates of the percentage of deaths attributable to suicide in patients with affective disorders range from 2% to nearly 20%.^{2–5}

Because of the complexity of bipolar disorder, medication treatment alone is often inadequate. Psychotherapy, especially cognitive-behavioral techniques that focus on compliance education about the illness, and maintaining circadian integrity (with social rhythm training) improve the effectiveness of medication. In fact, the difference in efficacy between medication alone versus medication plus psychotherapy⁶ can be greater than the difference between

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Table 1. General Principles of the Management of Bipolar Disorder

Monitor patient's course with a life chart
Treat substance abuse and side effects vigorously
Focus psychotherapy on compliance, psychoeducation, and circadian integrity
Continuously watch for suicidal behavior
Use antidepressants cautiously because they may induce mania or cycling
Prescribe combination therapy for the many patients who are unresponsive to monotherapy

medication alone versus placebo.⁷ Finally, we should move beyond the derogatory term “polypharmacy” and accept the reality that as for complex medical illnesses such as hypertension, a combination of medications is often more effective than monotherapy in bipolar disorder.

EVIDENCE FOR LITHIUM IN BIPOLAR DISORDER

A recent meta-analysis by Baldessarini and colleagues⁸ of 28 studies including nearly 3000 patients, 78.4% of whom had bipolar disorder, recurrent mania, or schizoaffective disorder, underlines the reality that lithium is still a first-line agent for the maintenance treatment of manic-depressive illness. In the 26 studies in which patients were observed for at least 1 month while not taking lithium, the risk of recurrence of a hypomanic, manic, or depressive episode was 3.2-fold lower for individuals taking lithium than for those who were not. The reduction in the risk of recurrence was even greater—a 3.6-fold difference—in the 11 placebo-controlled, parallel-group (i.e., “gold standard”) studies. Baldessarini et al. found that there was no difference in lithium's effectiveness when they compared the trials that involved withdrawing some of the patients from lithium treatment before randomly assigning them to placebo with the trials that did not involve prior lithium withdrawal. This finding contradicts the widely held belief that earlier lithium trials produced an exaggerated impression of lithium's effectiveness because the severity of illness would be increased for patients in the placebo group who were undergoing lithium withdrawal.

Although many trials have demonstrated the efficacy of lithium maintenance treatment, results of some trials⁹⁻¹¹ conducted in the United States in the 1990s seemed to indicate that lithium was no longer working. In a naturalistic study of 73 patients with mania and 66 with unipolar depression who had been hospitalized 1.7 years earlier, Harrow and colleagues¹⁰ found that when the patients who had been taking lithium for the entire year before follow-up were compared with those who had not taken lithium for the entire year, outcomes were similar, that is, around 40% of the patients in both groups had at least 1 manic episode. Tohen et al.¹¹ reported similar results in a study of 24 patients followed up 4 years after they recovered from their

first manic episode and were referred back to the community for care: only 46% of the patients were stable, and the type of medication prescribed, including lithium, was unrelated to patients' outcome.

Two different kinds of factors seem to explain the reported decline in lithium response rates in recent years in the United States: (1) changes in the illness and (2) changes in the nature of lithium research. Regarding changes in the illness, the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) definition of bipolar disorder has been broadened in the DSM-IV¹² to include more psychotic features. The median age at onset in the United States has decreased from 32 years in the 1960s and 1970s to less than 20 years by 1990.² Furthermore, comorbid substance abuse increased from about 20% in the 1960s¹³ to between 50% and 60% in 1990.¹ In addition, exposure to antidepressants has increased in the last 10 to 15 years as many new antidepressants have appeared on the market. In fact, a recent study¹⁴ found that 78% (N = 42) of 54 patients with bipolar disorder had received antidepressants sometime during their lives, but only 56% (N = 30) had taken a mood stabilizer ($\chi^2 = 6.087$, $df = 1$, $p = .014$). Antidepressant treatment may affect the course of a patient's bipolar disorder by contributing to a switch into mania or hypomania or precipitating rapid cycling.¹⁴

The second issue bearing on the reported decline in lithium's effectiveness in the United States is the changing nature of lithium studies. Since the 1990s, studies of lithium in the United States have often been conducted by investigators who have had more options for the treatment of bipolar disorder and have, therefore, been less well trained in the use of lithium than were their predecessors. Also, because studies in the 1990s came from university tertiary centers heavily dependent on referrals, nonclassical bipolar disorder less likely to respond well to lithium monotherapy was overrepresented in the study samples. Many lithium-responsive patients are successfully treated in the community, and there is no incentive to refer them to a research center. This overrepresentation of lithium nonresponders is simply an instance of the old adage in medicine that the longer a successful treatment is available in the community, the more difficult it is for researchers to show that it still works.

As research has shown more treatments to be effective in bipolar disorder, especially in the increasing number of patients with nonclassical features such as an early age at onset, substance abuse, and psychotic symptoms, the prescription of lithium monotherapy has decreased in the United States, while the prescription of divalproex monotherapy and divalproex plus lithium for bipolar disorder has increased.¹⁵ The shift in prescribing patterns may also be influenced by the U.S. practice of continuing antimanic agents for maintenance treatment, which is probably reinforced by the time pressures imposed by managed care, instead of making decisions about maintenance treatment

Table 2. Evidence of Efficacy for Medications in Treating Specific Symptoms of Bipolar Disorder^a

Drug	Acute Mania	Prophylaxis	Prophylaxis of Rapid Cycling	Breakthrough Depression
Carbamazepine	✓	?	?	?
Divalproex	✓	?	?	?
Lamotrigine	?	✓	✓	✓
Lithium	✓	✓	?	✓
Olanzapine	✓	?	?	✓

^aSymbols: ✓ = established by 1 or more randomized, placebo-controlled trials, ? = suggested by open and/or non-placebo-controlled trials.

separately from those about acute treatment, which should be done and is done by most clinicians in other countries. Perhaps the most important force shifting attention away from lithium and toward other treatments is the major role that the pharmaceutical industry plays in medical education. In general, in my opinion, the industry makes a positive contribution educationally, except when expensive patent-protected products compete with a generic drug like lithium, which is allotted virtually no money for continuing medical education or marketing. This neglect of lithium dangerously skews physicians' perceptions of lithium and is especially problematic for residency training. This decrease in the training of residents in the United States in how to use lithium has led to the misperception that lithium is difficult to use and has many more side effects than other treatments for bipolar disorder, although neither perception is supported by the literature.

LITHIUM IN THE CONTEXT OF OTHER MOOD STABILIZERS

Many different medications have been examined in all aspects of bipolar disorder. Although several agents are effective in different phases of the illness, no agent has been proven in randomized, placebo-controlled trials to treat both acute manic and depressive episodes and to prevent recurrences of both types of episodes, with or without rapid cycling (Table 2).

General Prophylaxis

For overall prophylaxis of bipolar disorder, lithium has by far the most evidence from placebo-controlled trials. In the 11 randomized, parallel-group studies included in the recent meta-analysis by Baldessarini and colleagues,⁸ the rate of relapse with placebo averaged 3.6 times higher than the rate in the group taking lithium. Overall, double-blind comparisons¹⁶⁻²¹ of lithium and carbamazepine generally show lithium to be superior for typical cases of bipolar disorder. A 52-week, placebo-controlled comparison of lithium and divalproex²² maintenance treatment in 372 patients with bipolar disorder failed to find significant differences from placebo for either drug on the primary outcome measure, time to any mood episode, but divalproex

did separate from placebo in some secondary analyses such as recurrence rates of mood episodes leading to discontinuation. Also, patients in the divalproex arm stayed in the trial significantly ($p = .02$) longer than those taking lithium, but this finding is difficult to interpret because the blood lithium levels were high for a maintenance trial and, therefore, increased the likelihood of side effect-related dropouts. Preliminary results²³ of an 18-month, placebo-controlled study in 175 outpatients with bipolar I disorder demonstrated that both lamotrigine and lithium were associated with significantly ($p \leq .02$) longer time to intervention for any mood episode than was placebo.

Mania

The discovery of lithium's antimanic efficacy launched the psychopharmacology revolution over 50 years ago. Other medications approved by the U.S. Food and Drug Administration (FDA) for the treatment of acute mania are divalproex and olanzapine. Agents such as the typical antipsychotics, other anticonvulsants (e.g., carbamazepine, gabapentin, topiramate, and oxcarbazepine), and other atypical antipsychotics (e.g., risperidone, quetiapine, clozapine, and ziprasidone) have varying levels of data on acute mania (many as add-ons) but have not yet received FDA approval.

It is important to note that no single drug works best for all manic patients. For example, in a pivotal trial by Bowden et al.,²² divalproex and lithium had, on average, nearly identical improvement rates versus placebo, patients who had previously responded to lithium treatment did not respond well to divalproex, and those with a history of lithium nonresponse had greater improvement with divalproex compared with previous lithium responders. Bowden et al. also found that among patients with mixed mania, divalproex was superior to lithium but for patients with classic mania (i.e., symptoms such as euphoria and grandiosity), lithium performed better than did divalproex. This principle of specific improvement by drug class seems also to hold true for maintenance treatment, but data are sparse.

Rapid Cycling

Compared with patients without rapid cycling, those with rapid cycling respond less well to any medication regimen. Although studies²⁴⁻²⁶ have shown that fewer patients with rapid cycling have a good or partial prophylactic response to lithium than do patients without rapid cycling (60% to 77% versus 0% to 28%), this difference in efficacy may be minimized in patients who do not receive antidepressants while on lithium therapy.²⁶ Although there are no controlled studies of divalproex in rapid cycling, open trials^{27,28} suggest that divalproex alone or in combination with another agent may prevent manic episodes in about 75% of rapid-cycling patients, depressive episodes in about 35%, and mixed states in about 95%. In a meta-analysis of 23 trials of carbamazepine in nonhomo-

Table 3. Ease of Lithium and Divalproex Use

Medical issue	Lithium	Divalproex
Medical monitoring	Renal, thyroid, and dermatologic	Hepatic, hematopoietic, pancreatic, and possibly polycystic ovary syndrome or testosterone level
Drug interactions	With thiazide diuretics, nonsteroidal antiinflammatory agents, angiotensin-converting enzyme inhibitors, xanthines, metronidazole, and calcium channel blockers	With lamotrigine, carbamazepine, aspirin, diazepam, fluoxetine, dicumarol, and phenobarbital

geneous cohorts with a total of 196 rapid-cycling patients, Calabrese et al.²⁹ found prophylactic response rates of 57% for depression and 59% for mania. The only mood stabilizer to have been studied in a randomized, placebo-controlled trial with rapid cyclers is lamotrigine.³⁰ In this trial, among 324 individuals with rapid-cycling bipolar I or II disorder, significantly ($p = .03$) more of the 60 patients who were stable without relapse for 6 months had taken lamotrigine (37 of 90 patients) rather than placebo (23 of 87 patients). The overall significance was caused by primarily lamotrigine's robust prophylactic effect among the bipolar II rapid cyclers.

Breakthrough Depression

Few agents have evidence for efficacy in breakthrough depression, which is depression that occurs during maintenance treatment and is, therefore, often associated with poor compliance. Zornberg and Pope³¹ reported that in 5 placebo-controlled trials³²⁻³⁶ of lithium in bipolar depression, 63 of the 80 patients (79%) taking lithium responded, with 29 of the patients (36%) considered unequivocal responders. There are no placebo-controlled trials of divalproex in bipolar depression. The agent with the most robust effect on bipolar depression is lamotrigine. In a large randomized, placebo-controlled study of patients with bipolar I depression, compared with those taking placebo, significantly ($p < .05$) more of the patients taking 200 mg/day of lamotrigine responded (51% vs. 26%). However, in the lamotrigine and lithium comparison,²³ only lamotrigine was significantly ($p = .015$) superior to placebo for time to intervention for a depressive episode.

Sanger et al.³⁷ analyzed the effects of olanzapine on bipolar depression in a 49-week, open-label, continuation-phase study of 113 patients with bipolar I disorder who had participated in a 3-week, placebo-controlled, double-blind study on acute mania. From baseline to endpoint, patients taking olanzapine experienced a significant ($p < .001$) improvement in 21-item Hamilton Rating Scale for Depression scores, with significantly ($p = .013$) greater improvement seen in patients with pure mania than mixed symptoms. More recently, the effect of olanzapine in bipolar depression ($p < .001$ vs. placebo) has been demonstrated in a large placebo-controlled trial,³⁸ but the size of the effect is about half that seen with lamotrigine and about the same as shown for lithium in earlier studies.

Results of a double-blind, placebo-controlled trial³⁹ of carbamazepine showed that 5 of 13 patients (38%) experi-

enced substantial improvement in depressive symptoms. In a double-blind, placebo-controlled trial,⁴⁰ lithium augmentation of carbamazepine induced response in 6 of 13 bipolar depressed patients and both of the unipolar depressed patients who had not responded to carbamazepine monotherapy.

EASE OF USE

Before prescribing lithium or another mood stabilizer, physicians should consider medical issues such as monitoring requirements, drug interactions, safety in pregnancy, the toxic-therapeutic ratio, side effects, and impact on mortality as well as cost. Both lithium and divalproex require medical monitoring and can have interactions with several drugs (Table 3). Although both drugs should be used with caution in pregnant women, especially during the first trimester, lithium may be safer than divalproex during pregnancy. Cohen et al.⁴¹ found that the risk ratios for congenital anomalies in 2 cohort studies of women whose children were exposed to lithium in utero were 1.5 (95% CI = 0.4 to 6.8)⁴² and 3.0 (95% CI = 1.2 to 7.7),⁴³ which were lower than previous estimates. In an analysis of data in 192 children prenatally exposed to anticonvulsants and 158 controls from European studies, Samrén et al.⁴⁴ reported that the relative risk of developing a major congenital malformation was 2.3 (95% CI = 1.2 to 4.7) with any anticonvulsant and 4.9 (95% CI = 1.3 to 18.0) with divalproex.

With respect to toxic-therapeutic ratio, divalproex, which can cause severe toxicity at about 3 times the average dose, has a greater margin of safety than does lithium, which can cause toxicity at twice the therapeutic dose.

Although some side effects are more common with lithium, others are more common with other mood stabilizers. In a 1-year, double-blind, randomized, placebo-controlled, parallel-group comparison²² of lithium and divalproex monotherapy in 369 patients with bipolar disorder, the occurrence of reported side effects besides tremor was substantially different in the lithium and divalproex groups. Significantly ($p \leq .01$) more patients in the lithium group than in the divalproex group experienced polyuria and polydipsia, and significantly ($p \leq .02$) more patients in the divalproex group experienced sedation, infection, and tinnitus. There were strong trends for more gastrointestinal side effects with lithium and more weight gain and hair loss with divalproex. These mixed results indicate that neither drug has a clear advantage with respect to side effects.

In a randomized, multicenter, 2.5-year trial⁴⁵ comparing lithium and carbamazepine in 144 patients with bipolar disorder, significantly ($p = .004$) more patients in the lithium group reported having experienced slight to moderate adverse events when side effects were subjectively measured at the end of the trial. However, fewer patients taking lithium than those taking carbamazepine discontinued medication because of an adverse event (4 vs. 9 patients), and the rate of satisfaction related to medication side effects was 80% to 85% in both treatment groups. Overall, lithium does not appear to have a more negative side effect profile than agents such as divalproex or carbamazepine. Also, slow-release formulations of lithium may be more tolerable than immediate-release formulations. Slow-release lithium has been shown to have fewer gastrointestinal side effects⁴⁶ and may have fewer renal effects.⁴⁷

Whether a mood stabilizer reduces mortality rates is also an important consideration in bipolar disorder, which is associated with a high suicide rate. In a meta-analysis of 33 studies in 13,725 patients with bipolar, major affective, or schizoaffective disorder, Baldessarini et al.⁴⁸ reported that lithium reduces suicidal behavior and, therefore, the morbidity and mortality associated with mood disorders. When compared with rates for patients not taking lithium, the rate of completed suicides was 4.75-fold lower for patients taking lithium. Nothing is known about the effects of divalproex on suicidal behavior.

The cost of medication favors lithium, which is cheaper than divalproex. Weighing medical issues and costs will help determine which drug or drug combination is optimal for each individual with bipolar disorder.

BENEFITS OF COMBINING LITHIUM WITH OTHER AGENTS

Although the results of a meta-analysis⁸ of 28 studies involving 2985 patients showed that lithium is an efficacious treatment for bipolar disorder, the mean reduction in risk of a recurrent affective episode was only 54.9% during a period of 5.9 years. Therefore, combining lithium treatment with another agent may increase a patient's time well. Results from the comparison²³ of lamotrigine and lithium suggest that these 2 agents have complementary actions: lamotrigine has a greater effect on depression than mania, and lithium has a greater effect on mania.

Research has also found that predictors of antimanic and prophylactic response to lithium vary from predictors of response to anticonvulsants such as divalproex and carbamazepine. Patients who respond to lithium often have typical manic symptoms such as euphoria and grandiosity, an episode sequence of mania-depression-free interval, a fully remitting course, i.e., a return to a normal baseline between episodes, and a family history of bipolar disorder.^{19,49} Response to divalproex or carbamazepine may be predicted by mixed states, rapid cycling, comorbid sub-

stance abuse, psychotic features, and secondary mania such as mania related to neurologic conditions or head injuries.⁵⁰ Documenting the course of a patient's illness with a life chart will help the physician identify the patient's predictors of response and select the best agent or combination of agents for that patient.

Patients taking lithium in combination with other mood stabilizers often experience greater improvement than do patients taking either mood stabilizer alone. Open trials⁵¹⁻⁵⁴ of patients with bipolar disorder have shown that the combination of lithium and divalproex may be both safe and more effective than monotherapy. In a 3-year, double-blind trial,⁵⁵ 52 patients with bipolar disorder were randomly assigned to treatment with each of the following for 1 year: carbamazepine monotherapy, lithium monotherapy, and carbamazepine and lithium combination therapy. According to Clinical Global Impressions scale scores, the percentage of patients with moderate or marked improvement was 33.3% for lithium monotherapy, 31.4% for carbamazepine monotherapy, and 55.2% for combination therapy. Although significantly greater improvement was seen with combinations of lithium and divalproex or carbamazepine, combining lithium with olanzapine in a 6-week, double-blind, randomized trial⁵⁶ of 324 patients with bipolar disorder did not result in significantly better rating scale scores than did lithium monotherapy.

Besides often greater efficacy, another advantage of using a combination of lithium and another mood stabilizer in bipolar disorder is that lithium and other mood stabilizers have somewhat different side effect profiles. A combination of lithium and an anticonvulsant might result in fewer side effects than would monotherapy because both drugs can be given at a lower dose since evidence shows that lithium and anticonvulsants appear to act synergistically at postsynaptic signal transducer sites.

The complementary efficacy and different side effect profiles of lithium and an anticonvulsant such as divalproex may help to increase patients' compliance. In a 1-year study of 144 patients who had been hospitalized for a manic or a mixed episode of bipolar disorder, Keck et al.⁵⁷ found that 59% of patients on lithium monotherapy and 48% on divalproex monotherapy were compliant with their medication regimen. However, among the patients who received both lithium and divalproex, the compliance rate was 100%. The high efficacy associated with this medication combination is thought to have contributed to the 100% compliance rate, that is, the ratio of benefits to side effects was perhaps higher than that associated with monotherapy.

RECOMMENDED DOSING OF LITHIUM

Because lithium may be toxic at twice the therapeutic dose, physicians must adhere to treatment guidelines for

lithium by monitoring patients for plasma lithium levels and performing yearly checks of creatinine, thyroxine (T_4), and thyroid-stimulating hormone levels. What is the optimal blood level for lithium monotherapy? In a 2-year, prospective study, Maj et al.⁵⁸ maintained 69 patients at 1 of 4 plasma levels of lithium: 0.30–0.45, 0.46–0.60, 0.61–0.75, or 0.76–0.90 mEq/L. The 0.30–0.45 mEq/L group experienced only insignificant improvement after starting lithium, and the 0.76–0.90 group experienced significantly more side effects than the other 3 groups. Therefore, considering both risks and benefits, Maj et al. recommended plasma lithium levels of 0.46–0.75 mEq/L for prophylaxis of bipolar disorder. Clinical experience has also led to the common practice of dosing lithium to achieve moderate plasma levels between 0.6 and 0.8 mEq/L instead of 1.0 mEq/L, as was common in the 1960s and 1970s. However, further research on the outcomes of moderate doses of lithium is needed. Lower doses may be sufficient to stabilize patients with bipolar II disorder or recurrent unipolar disorder and patients concurrently receiving another mood stabilizer or an antidepressant, and higher doses may be needed for patients with bipolar I disorder. Some clinicians also speculate from their experience that patients who have been stabilized with lithium maintenance treatment may require lower doses to remain stable the longer they take the drug.

Although the plasma drug level is a usable guide for determining the optimal dose of lithium for a patient, the intracellular level is the true indicator. The ratio of intracellular to plasma drug level varies from patient to patient. For example, older or female patients may achieve higher intracellular concentrations with low plasma drug levels than would younger or male patients. As patients get older and their renal excretion becomes less efficient, their dose of lithium may have to be decreased to avoid side effects. Therefore, when choosing an appropriate dose of lithium, clinicians should consider not only the plasma level but also the other factors, such as diet, exercise habits, clinical state, age, medical illnesses, drug use, and pregnancy status, that influence a patient's tolerability of lithium. For patients whose life chart predicts that warning signs such as decreased need for sleep and grandiose behavior will precede a full manic episode and whose condition is reliably monitored for changes by themselves or their family members, lower plasma lithium levels may be tried over time. Greater caution should be used when attempting to lower the plasma lithium level in patients whose history suggests that they switch suddenly, that is, go to sleep in one state and wake up in the other.

CONCLUSION

Lithium is the mood stabilizer with the most evidence of efficacy in the acute and maintenance treatment of bipolar disorder, especially in patients with a history of nor-

mal free intervals between manic and depressive episodes. However, as nonclassical features of bipolar disorder, including mixed states related to substance abuse and antidepressant-induced mania, are seen more commonly in clinical practice, the use of newer mood stabilizers such as divalproex, carbamazepine, and olanzapine has become more widespread. Although clinicians who were trained in the 1970s and 1980s are comfortable controlling bipolar disorder with lithium, many young clinicians assume that lithium is of only historical interest and prescribe anticonvulsants as a standard treatment for bipolar disorder. Because fewer clinicians are being instructed in the use of lithium, some patients who would respond to lithium are not given this treatment option. Examining the characteristics of each patient's illness will help physicians choose the proper treatment for each case of bipolar disorder. Some patients may respond best to lithium monotherapy and some to monotherapy with a different mood stabilizer. However, the optimal treatment choice for many patients with bipolar disorder, especially those with complex courses, a high incidence of side effects, or problems with compliance, may be a combination of lithium and another mood stabilizer.

Drug names: carbamazepine (Eptol, Tegretol, and others), clozapine (Clozaril and others), diazepam (Diastat, Valium, and others), divalproex (Depakote), fluoxetine (Prozac and others), gabapentin (Neurontin), lamotrigine (Lamictal), metronidazole (Flagyl, Metromidol, and others), olanzapine (Zyprexa), oxcarbazepine (Trileptal), quetiapine (Seroquel), risperidone (Risperdal), topiramate (Topamax), ziprasidone (Geodon).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, carbamazepine is not approved by the U.S. Food and Drug Administration for the treatment of bipolar disorder; divalproex is not approved for the maintenance treatment of bipolar disorder; clozapine, gabapentin, oxcarbazepine, quetiapine, risperidone, topiramate, and ziprasidone are not approved for the treatment of mania; and lamotrigine is not approved for the treatment of bipolar depression.

REFERENCES

1. Regier DA, Farmer ME, Rae DS, et al. Comorbidity of mental disorders with alcohol and other drug abuse. *JAMA* 1990;264:2511–2518
2. Goodwin FK, Jamison KR. *Manic-Depressive Illness*. New York, NY: Oxford University Press; 1990
3. Inskip HM, Harris EC, Barraclough B. Lifetime risk of suicide for affective disorder, alcoholism and schizophrenia. *Br J Psychiatry* 1998;172:35–37
4. Bostwick JM, Pankratz VS. Affective disorders and suicide risk: a reexamination. *Am J Psychiatry* 2000;157:1925–1932
5. Brodersen A, Licht RW, Vestergaard P, et al. Sixteen-year mortality in patients with affective disorder commenced on lithium. *Br J Psychiatry* 2000;176:429–433
6. Keller MB, McCullough JP, Klein DN, et al. Comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. *N Engl J Med* 2000;342:1462–1470
7. Feighner J, Targum SD, Bennett ME, et al. A double-blind, placebo-controlled trial of nefazodone in the treatment of patients hospitalized for major depression. *J Clin Psychiatry* 1998;59:246–253
8. Baldessarini RJ, Tondo L, Hennen J, et al. Is lithium still worth using? an update of selected recent research. *Harv Rev Psychiatry* 2002;10:59–75
9. Solomon RL, Rich CL, Darko DF. Antidepressant treatment and the occurrence of mania in bipolar patients admitted for depression. *J Affect Disord* 1990;18:253–257

10. Harrow M, Goldberg JF, Grossman LS, et al. Outcome in manic disorders: a naturalistic follow-up study. *Arch Gen Psychiatry* 1990;47:665–671
11. Tohen M, Watermaux CM, Tsuang MT, et al. Four-year follow-up of twenty-four first-episode manic patients. *J Affect Disord* 1990;19:79–86
12. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Washington, DC: American Psychiatric Association; 1994
13. Mayfield DG, Coleman LL. Alcohol use and affective disorder. *Dis Nerv Syst* 1968;29:467–474
14. Ghaemi SN, Boiman EE, Goodwin FK. Diagnosing bipolar disorder and the effect of antidepressants: a naturalistic study. *J Clin Psychiatry* 2000; 61:804–808
15. Fenn HH, Robinson D, Luby V, et al. Trends in pharmacotherapy of schizoaffective and bipolar affective disorders: a 5-year naturalistic study. *Am J Psychiatry* 1996;153:711–713
16. Luszcz RM, Murphy DP, Nunn CM. Carbamazepine vs lithium in the treatment and prophylaxis of mania. *Br J Psychiatry* 1988;153:198–204
17. Coxhead N, Silverstone T, Cookson J. Carbamazepine versus lithium in the prophylaxis of bipolar affective disorder. *Acta Psychiatr Scand* 1992;85: 114–118
18. Greil W, Kleindienst N. The comparative prophylactic efficacy of lithium and carbamazepine in patients with bipolar I disorder. *Int Clin Psychopharmacol* 1999;14
19. Kleindienst N, Greil W. Differential efficacy of lithium and carbamazepine in the prophylaxis of bipolar disorder: results of the MAP study. *Neuropsychobiology* 2000;42(suppl 1):2–10
20. Okuma T, Yamashita I, Takahashi R, et al. Comparison of the antimanic efficacy of carbamazepine and lithium carbonate by double-blind controlled study. *Pharmacopsychiatry* 1990;23:143–150
21. Kleindienst N, Greil W. Inter-episodic morbidity and drop-out under carbamazepine and lithium in the maintenance treatment of bipolar disorder. *Psychol Med* 2002;32:493–501
22. Bowden CL, Calabrese JR, McElroy SL, et al. A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. *Arch Gen Psychiatry* 2000;57:481–489
23. Calabrese JR, Bowden CL, DeVaugh-Geiss J, et al. Lamotrigine demonstrates long-term mood stabilization in manic patients. In: *New Research Abstracts of the 154th Annual Meeting of the American Psychiatric Association*; New Orleans, La
24. Dunner DL, Fieve RR. Clinical factors in lithium carbonate prophylaxis failure. *Arch Gen Psychiatry* 1974;30:229–233
25. Prien RF, Caffey EM Jr, Klett CJ. Factors associated with treatment success in lithium carbonate prophylaxis: report of the Veterans Administration and National Institute of Mental Health collaborative study group. *Arch Gen Psychiatry* 1974;31:189–192
26. Kukopulos A, Reginaldi D, Laddomada P, et al. Course of the manic-depressive cycle and changes caused by treatment. *Pharmakopsychiatr Neuropsychopharmacol* 1980;13:156–167
27. Calabrese JR, Delucchi GA. Spectrum of efficacy of valproate in 55 patients with rapid-cycling bipolar disorder. *Am J Psychiatry* 1990;147: 431–434
28. Calabrese JR, Markovitz PJ, Kimmel SE, et al. Spectrum of efficacy of valproate in 78 rapid-cycling bipolar patients. *J Clin Psychopharmacol* 1992; 12(suppl 1):53S–56S
29. Calabrese JR, Bowden C, Woynshville MJ. Lithium and anticonvulsants in bipolar disorder. In: Bloom FE, Kupfer DJ, eds. *Psychopharmacology: The Fourth Generation of Progress*. New York, NY: Raven Press; 1994: 1099–1111
30. Calabrese JR, Suppes T, Bowden CL, et al. A double-blind, placebo-controlled, prophylaxis study of lamotrigine in rapid-cycling bipolar disorder. *J Clin Psychiatry* 2000;61:841–850
31. Zornberg GL, Pope HG. Treatment of depression in bipolar disorder: new directions for research. *J Clin Psychopharmacol* 1993;13:397–408
32. Goodwin FK, Murphy DL, Bunney WE Jr, et al. Lithium-carbonate treatment in depression and mania. A longitudinal double-blind study. *Arch Gen Psychiatry* 1969;21:486–496
33. Goodwin FK, Murphy DL, Dunner DL, et al. Lithium response in unipolar versus bipolar depression. *Am J Psychiatry* 1972;129:44–47
34. Noyes R Jr, Dempsey GM, Blum A, et al. Lithium treatment of depression. *Compr Psychiatry* 1974;15:187–193
35. Baron M, Gershon ES, Rudy V, et al. Lithium carbonate response in depression: prediction by unipolar/bipolar illness, average-evoked response, catechol-O-methyl transferase, and family history. *Arch Gen Psychiatry* 1975;32:1107–1111
36. Mendels J. Lithium in the treatment of depression. *Am J Psychiatry* 1976; 133:373–378
37. Sanger TM, Grundy SL, Gibson PJ, et al. Long-term olanzapine therapy in the treatment of bipolar I disorder: an open-label continuation phase study. *J Clin Psychiatry* 2001;62:273–281
38. Baker RW, Vieta E, Ketter TA, et al. Olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar depression [poster]. Presented at the 41st annual meeting of the American College of Neuropsychopharmacology; Dec 10, 2002; San Juan, Puerto Rico
39. Ballenger JC, Post RM. Carbamazepine in manic-depressive illness: a new treatment. *Am J Psychiatry* 1980;137:782–790
40. Kramlinger KG, Post RM. The addition of lithium to carbamazepine: antidepressant efficacy in treatment-resistant depression. *Arch Gen Psychiatry* 1989;46:794–800
41. Cohen LS, Friedman JM, Jefferson JW, et al. A reevaluation of risk of in utero exposure to lithium. *JAMA* 1994;271:146–150
42. Jacobson SJ, Jones K, Johnson K, et al. Prospective multicentre study of pregnancy outcome after lithium exposure during first trimester. *Lancet* 1992;339:530–533
43. Kallen B, Tandberg A. Lithium and pregnancy: a cohort study on manic-depressive women. *Acta Psychiatr Scand* 1983;68:134–139
44. Samrén EB, van Duijn CM, Koch S, et al. Maternal use of antiepileptic drugs and the risk of major congenital malformations: a joint European prospective study of human teratogenesis associated with maternal epilepsy. *Epilepsia* 1997;38:981–990
45. Greil W, Ludwig-Mayerhofer W, Erazo N, et al. Lithium versus carbamazepine in the maintenance treatment of bipolar disorders: a randomised study. *J Affect Disord* 1997;43:151–161
46. Grof P, MacCrimmon D, Saxena B, et al. Bioavailability and side effects of different lithium carbonate products. *Neuropsychobiology* 1976;2: 313–323
47. Miller AL, Bowden CL, Plewes J. Lithium and impairment of renal concentrating ability. *J Affect Disord* 1985;9:115–119
48. Baldessarini RJ, Tondo L, Hennen J. Treating the suicidal patient with bipolar disorder: reducing suicide risk with lithium. *Ann N Y Acad Sci* 2001;932:24–38; discussion 39–43
49. Grof P, Alda M, Grof E, et al. The challenge of predicting response to stabilising lithium treatment: the importance of patient selection. *Br J Psychiatry* 1993;163(suppl 21):16–19
50. Bowden CL. Clinical correlates of therapeutic response in bipolar disorder. *J Affect Disord* 2001;67:257–265
51. Schneider AL, Wilcox CS. Divalproate augmentation in lithium-resistant rapid cycling mania in four geriatric patients. *J Affect Disord* 1998;47: 201–205
52. Solomon DA, Ryan CE, Keitner GI, et al. A pilot study of lithium carbonate plus divalproex sodium for the continuation and maintenance treatment of patients with bipolar I disorder. *J Clin Psychiatry* 1997;58:95–99
53. Mitchell P, Withers K, Jacobs G, et al. Combining lithium and sodium valproate for bipolar disorder. *Aust N Z J Psychiatry* 1994;28:141–143
54. Sharma V, Persad E, Mazmanian D, et al. Treatment of rapid cycling bipolar disorder with combination therapy of valproate and lithium. *Can J Psychiatry* 1993;38:137–139
55. Denicoff KD, Smith-Jackson EE, Disney ER, et al. Comparative prophylactic efficacy of lithium, carbamazepine, and the combination in bipolar disorder. *J Clin Psychiatry* 1997;58:470–478
56. Tohen M, Chengappa KN, Suppes T, et al. Efficacy of olanzapine in combination with valproate or lithium in the treatment of mania in patients partially nonresponsive to valproate or lithium monotherapy. *Arch Gen Psychiatry* 2002;59:62–69
57. Keck PE Jr, McElroy SL, Strakowski SM, et al. Compliance with maintenance treatment in bipolar disorder. *Psychopharmacol Bull* 1997;33:87–91
58. Maj M, Starace F, Nolfi G, et al. Minimum plasma lithium levels required for effective prophylaxis in DSM III bipolar disorder: a prospective study. *Pharmacopsychiatry* 1986;19:420–423