Rationale for Long-Term Treatment of Bipolar Disorder and Evidence for Long-Term Lithium Treatment

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Because of the great morbidity and mortality associated with bipolar disorder, long-term treatment is necessary to prevent recurrence and reduce the loss of productivity and increased medical costs associated with this illness. The agent with the most evidence of efficacy and the only U.S. Food and Drug Administration–approved medication for maintenance treatment of bipolar disorder is lithium. Lithium may cause a prophylactic response in more than two thirds of patients with bipolar disorder and reduce suicide risk by more than 8-fold. However, lithium may be more effective for patients with classical features such as fully remitting courses and typical manic symptoms than for patients with nonclassical bipolar features such as mixed states and rapid cycling. Because lithium may be toxic at only twice the therapeutic dose, physicians should consider patients' ages and medical history when prescribing this drug. Monitoring requirements; possible side effects; changes in the illness including more treatment-resistant forms; and the introduction of newer agents, which are supported by more marketing and continuing medical education programs than the essentially generic drug lithium, have contributed to the decline in lithium prescription rates in the last 15 years in the United States. However, long-term treatment with lithium continues to be effective in many patients, especially if the dose is periodically evaluated as patients experience changes in their physical health and lithium tolerance. Until newer agents have comparable evidence of efficacy, lithium will be considered a first-line long-term treatment for bipolar disorder, either as monotherapy or in combination therapy.

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RATIONALE FOR LONG-TERM TREATMENT FOR BIPOLAR DISORDER

From 0.9% to 2.1% of community samples have bipolar disorder,[1] which is chronic, relentless, and devastating without treatment. Manic episodes recur in more than 90% of individuals with bipolar disorder, and about 60% to 70% of manic and hypomanic episodes immediately precede or follow a major depressive episode.[1] The frequency of episodes also tends to increase with age. Despite the risk of recurrence, in the United States, there tends to be a focus on short-term treatment, perhaps because of the high mobility of the population. Unlike in other parts of the world with more stable populations such as Europe, Australia, and Canada, few clinicians in the United States have the luxury of getting to know and treat patients for their whole life cycle. However, the percentage of patients receiving long-term treatment for bipolar disorder may be increasing as more clinical trials demonstrate the benefits.

Long-term treatment for bipolar disorder is needed because of the burden this disease creates for the millions of affected patients (Table 1). Many patients with bipolar disorder, especially those with bipolar II disorder or rapid cycling, continue to experience subthreshold symptoms even after recovering from a full mood episode. A naturalistic study by Gitlin and colleagues[4] showed high rates of morbidity even during maintenance therapy among patients referred to a tertiary case academic health center. Of 82 patients with bipolar disorder who were treated for at least 2 years, 29.3% experienced significant symptoms during one fourth or more of the follow-up period. However, even in this relatively refractory population, the frequency, number, and severity of episodes are lower with prophylactic therapy than with no treatment. A recent meta-analysis of 12 placebo-controlled trials[5] found that the rate of relapse averaged 3.6 times higher for patients on placebo compared with those receiving long-term lithium therapy. Problems with compliance continue to limit the effectiveness of long-term treatment since some patients decide they are well and see no more need for medication. It is important to continually emphasize that without treatment, patients with bipolar disorder may not be able to maintain normal functioning.

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Table 1. Reasons for Long-Term Treatment for Bipolar Disorder

Morbidity
6th leading cause for years lived with a disability[a]
Causes 1.0% of disability-life adjusted years[a]
$3416 (SD = $6862) in medical costs for bipolar patients vs $1462 (SD = $4469) for controls[b]
Mortality
10% to 15% rate of death by suicide[c]

[a]Data from Murray and Lopez.[2]
[b]Data from Simon and Unützer.[3]
[c]Data from the American Psychiatric Association.[1]

Untreated bipolar disorder also increases the financial burden associated with medical care costs. Extrapolating from the data of Simon and Unützer,[3] I estimated that the annual medical care costs of patients with bipolar disorder were more than double the costs of age-matched appropriate controls. Because 95% of health care expenses are now nonpsychiatric, restricting coverage for the 5% of costs that are psychiatric can significantly increase a person's total health care costs.

Long-term treatment might also reduce the death rate associated with bipolar illness. Bipolar disorder should be considered a lethal illness. The principal reasons for deaths attributed to bipolar disorder are suicide and cardiovascular illness. The proportion of deaths attributable to suicide in patients with bipolar disorder is estimated to range from 10% to 20%, and age-corrected estimates exceed the death rate of some chronic medical illnesses. The death rate from cardiovascular illness is related to the higher prevalence of cardiovascular illness in people with bipolar disorder than in the general population. One possible explanation for this higher prevalence is that functional disturbances in the membrane systems in the body that occur with bipolar disorder contribute to some of the comorbid illnesses such as cardiovascular disease and diabetes. Another explanation is that, because of their illness, people with bipolar disorder do not take as good care of themselves as do the general population. These individuals with bipolar disorder have more erratic diets, often have substance use disorders, and exercise less often—all of which can contribute to cardiovascular illness. However, effective long-term treatment can reduce the mortality rates from suicide and cardiovascular disease in patients with bipolar disorder.[6]

Physicians and patients should decide together whether long-term therapy is warranted. To help make this decision, the physician and patient can make a life chart including the number, type, and frequency of episodes; treatment history; and events that may have precipitated or occurred during episodes. Long-term treatment should be considered for patients who have had at least 2 mood episodes. In addition, the revised American Psychiatric Association[7] practice guidelines recommend that continuation and maintenance treatment be initiated after patients remit from a manic episode and considered for patients with bipolar II disorder. These guidelines also recommend which therapies are most effective for long-term treatment of patients with bipolar disorder (Table 2). Lithium and valproate are the maintenance medications recommended with the highest level of clinical confidence. In the case of lithium, this recommendation is supported by substantial evidence from controlled studies.

Table 2. American Psychiatric Association Practice Guidelines for Maintenance Treatment for Bipolar Disorder[a]

Maintenance Treatment Guideline	Level of Clinical Confidence
When warranted	
After a manic episode	I
After a depressive episode	II
Medication monotherapy	
Lithium	I
Valproate	I
Lamotrigine	II[b]
Carbamazepine	II[b]
Olanzapine	II[b]
Medication augmentation	
Additional maintenance medication	II
Atypical antipsychotic	III
Antidepressant	III
Psychotherapy	II
Support group	I
Electroconvulsive therapy	II[c]

[a]Data from the American Psychiatric Association.[7]
Symbols: I = substantial, II = moderate, III = varies with individual circumstances.
[b]Use as monotherapy if this medication was effective for acute treatment of the last episode (I).
[c]Consider its use during maintenance treatment if it was effective for acute treatment of the last episode (II).

Once long-term treatment has been initiated, patients' daily response can be evaluated by using the National Institute of Mental Health prospective Life Chart Methodology (NIMH-LCM-p), which uses the degree of functional impairment to determine the severity of mood episodes.[8] Engaging patients in evaluating their illness and treatment can encourage them to report any changes in the effectiveness or tolerability of their medication. Whether a drug is tolerable influences patients' compliance, and resistance to taking maintenance medication for years, if not the rest of one's life, may be the greatest contributor to noncompliance.[9] Physicians must explain to their patients the risk of recurrence without long-term treatment because no medication treatment is complete without psychosocial management and patient education.

LONG-TERM TREATMENT WITH LITHIUM

Lithium, which launched the psychopharmacology revolution over 50 years ago, is the original antimanic agent and is still the only drug approved as maintenance treatment for bipolar disorder by the U.S. Food and Drug Administration (FDA). In general, patients with typical

manic symptoms, a family history of bipolar disorder, or the episode sequence of mania-depression-free interval respond well to lithium.[10] Work by Grof et al.[11] suggests that patients who have fully remitting courses, i.e., a return to baseline between episodes—no matter how ill they are and what the characteristics of their acute mania are—have excellent responses to lithium. Still, patients with nonclassical features, e.g., mixed states, rapid cycling, comorbid substance abuse, psychotic features, and secondary mania, may respond better to newer treatments, particularly anticonvulsants such as carbamazepine and divalproex, or atypical antipsychotics, than to lithium monotherapy.

Lithium Literature

There are at least 3 different sets of literature about lithium: (1) the literature from the 1960s and 1970s, (2) the literature from the United States from the 1980s onward, and (3) the literature from the rest of the world from the 1980s until now. Comparing these bodies of literature is complicated. In the older lithium literature, there were essentially no other medication options, so older studies had more reported compliance, fewer dropouts, and patients with more typical symptoms than present-day studies. Outcome measures also differ between older and newer studies. Older studies did not report spectrum of efficacy data as primary or key secondary outcome measures and did not use survival analyses. In addition, while patients can no longer participate if they relapse during a newer study, older studies allowed patients who relapsed to continue in the study.

The differences in the 2 contemporary bodies of literature may explain why lithium is used more often in Europe than in the United States. Bipolar disorder has been studied and treated longer in Europe, and the stability of these European populations is more conducive to longitudinal observations. The newer U.S. studies, while employing more sophisticated methodologies than European and older U.S. studies, have had to confront the more difficult populations typically seen in academic tertiary referral centers; patients who have responded to lithium in the community are underrepresented in these research samples. Also, in contrast to the U.S. in the 1960s and 1970s, there are now more substance abuse, more use of antidepressants, and fragmented treatment because of increased mobility of the population. These features also tend to differentiate contemporary patients in the United States from comparative populations in Europe. While studies in Europe, Australia, and Canada often follow dropouts, studies in the United States generally do not. In their research in Italy, Maj and colleagues[12] followed dropouts and found that many subjects attributed their dropping out to factors other than nonresponse to lithium, e.g., feeling well, but deciding how to analyze this data can be difficult.

Individual studies in each of these 3 bodies of literature may also be divided into randomized, placebo-controlled trials and open trials, both of which have shown the prophylactic effectiveness of lithium in bipolar disorder. When making treatment decisions for individual patients, physicians should consider the findings from both randomized, placebo-controlled trials and open trials, which might more closely reflect actual clinical practice, albeit with more likelihood that bias will affect the results.

Lithium Prophylaxis

In *Manic-Depressive Illness*,[5] Jamison and I compared 10 major double-blind, placebo-controlled trials of lithium prophylaxis from the 1970s. In these studies, the overall relapse rate with lithium was 34% and without lithium, 81%. The mean duration of these studies was 20 months, and 9 of the 10 studies found lithium to have a statistically significant, favorable separation from placebo. In these studies, manic relapses were more common and more effectively prevented by lithium than were depressive relapses, although that finding is still controversial. One of these studies,[13] a double-blind, placebo-controlled trial with a discontinuation design, used a then unusual endpoint, the need for other medication or electroconvulsive therapy (ECT). The 28 patients receiving lithium in this study required significantly less antidepressant therapy and ECT and significantly fewer antimanic drugs than did the 37 patients receiving placebo.

Studies conducted in the past 20 years have also found long-term lithium treatment to be effective in patients with bipolar disorder. Page and colleagues[14] studied 101 patients consecutively admitted to a lithium clinic during a 5-year period. At the time of follow-up, 49% of them had a complete remission, that is, no episodes; 41% had a partial response, that is no hospitalizations; and 10% had no response. However, selection in this study may have been biased to lithium response and compliance. Maj and colleagues[12] also conducted a 5-year study of lithium prophylaxis in patients with bipolar disorder. I reanalyzed the data (F.K.G., unpublished data, 1999) from this study of 337 patients by considering only those patients whose response could be determined. For example, I excluded patients who dropped out of the study because they felt well or those whose clinical response was not reported before they dropped out because of side effects. Of the 278 patients whose response could be determined, 38% had a complete response, that is, no episodes, and 38% had a partial response, that is, a 50% or greater improvement in rating scale scores. As found in other studies, the patients who had complete responses had more typical bipolar features than did the patients who had a partial or no response.

Berghofer and colleagues analyzed the efficacy of lithium prophylaxis in a study[15] with a subsample of 30 patients treated with lithium for at least 10 years and another

Table 3. Studies Showing Differences in the Effect of Lithium on Features of Bipolar Disorder

Study	N	Feature	Finding
Dunner and Fieve[18]	55	Rapid cycling vs non–rapid cycling	18% of patients with rapid cycling responded vs 59% without rapid cycling
Prien et al[19]	91	Rapid cycling vs non–rapid cycling	No patients with rapid cycling responded vs 71% without rapid cycling
Kukopulos et al[20, a]	121	Rapid cycling vs non–rapid cycling	32% of patients with rapid cycling responded well vs 57% without rapid cycling
Greil et al[21]	86	Classical vs nonclassical bipolar symptoms	26% of patients with classical symptoms were hospitalized vs 44% with nonclassical symptoms
Tondo et al[22]	317	Bipolar I vs bipolar II	Mean improvement in 7 morbidity measures was 73.2% (SD = 13.3%) for patients with bipolar II vs 59.1% (SD = 12.7%) for those with bipolar I
		Mania vs depression	Patients had 3.3-fold fewer manic episodes per year vs 2.1-fold fewer depressive episodes

[a]Includes only patients with a continuous circular course. Rapid cycling was defined as 2 or more episodes per year.

study[16] of 22 patients who had been treated in a lithium clinic for at least 20 years. In both studies, the efficacy of lithium was not found to have diminished, even as doses were lowered over time. This finding raises the question of whether stability begets stability in long-term use, that is, whether patients may require lower levels of a drug after being treated with it for a long time, or whether the efficacy of lower doses is related to changes in tissue sensitivity as patients age.

Comparisons of lithium's effectiveness in both American and European trials have also been made. Baldessarini and colleagues[17] conducted a meta-analysis of 28 studies of lithium maintenance therapy in manic-depressive illness. In total, these studies represent nearly 3000 patients, 78.4% of whom had bipolar disorder. In all 28 studies, the risk of recurrence of an affective episode was lower on lithium, averaging 3.2-fold lower for patients taking lithium than for those who were not. In the 12 placebo-controlled, parallel-group studies included in this review, the risk of recurrence averaged 3.6-fold lower on lithium. The mean reduction in the risk of recurrence was about 65% for both the studies that involved lithium withdrawal prior to random assignment to placebo and those that did not.

Lithium and Bipolar Disorder Features

The effectiveness of lithium may depend on the features of the individual's bipolar disorder (Table 3). When the prophylactic efficacy of lithium was compared in individuals with and without rapid-cycling courses, studies from the 1970s[18,19] showed that those patients with rapid cycling had a less positive prophylactic response to lithium than those with less frequent episodes. One drawback of these studies is that patients with rapid cycling were outnumbered at least 4 to 1 by those without rapid cycling. In 56 patients without rapid cycling and 65 patients with rapid cycling, Kukopulos and colleagues[20] found a higher rate of response for the overall group of rapid-cycling patients than did previous studies. The authors examined whether this poor response to lithium among patients with rapid-cycling bipolar disorder may be related to the use of antidepressants. This analysis showed that while 8 (16%) of the 50 patients with rapid cycling who received antidepressant therapy during the study responded well to lithium, a rate similar to that in the other studies, in the 15 patients with rapid cycling who discontinued antidepressant therapy before beginning lithium, 13 (87%) responded well to lithium.

Greil et al.[21] compared the prophylactic efficacy of lithium and carbamazepine in patients with classical bipolar disorder, i.e., patients with bipolar I disorder who did not have comorbid conditions or mood-incongruent delusions, versus patients with nonclassical bipolar disorder. In the patients with classical bipolar disorder, there was a significantly lower number of hospitalizations for patients treated with lithium than for those treated with carbamazepine. Moreover, in patients treated with lithium, the number of hospitalizations was associated with nonclassical features, including bipolar II disorder, bipolar disorder not otherwise specified, and mixed states. This association was not found in patients treated with carbamazepine.

The relationship between the effectiveness of lithium and the types of bipolar disorder and the types of episodes was examined in a retrospective study by Tondo and colleagues,[22] which analyzed the clinical research records of 317 adults with bipolar disorder who were undergoing lithium maintenance treatment at a mood disorders research center in Italy. These patients were selected because they had not received long-term treatment with antidepressants, antipsychotics, or anticonvulsants and did not abuse drugs or alcohol. For patients on lithium therapy, the mean reduction in frequency of manic and depressive episodes was greater in the 129 patients with bipolar II disorder than in the 188 patients with bipolar I disorder.

In this trial there was not a great difference in the prophylactic effects of lithium on mania and depression. However, in a recent randomized, placebo-controlled trial, Calabrese and colleagues[23] compared lithium and lamotrigine in the prevention of mania and depression in 175

patients with bipolar I disorder. For the overall time to intervention for a mood episode, both drugs separated from placebo. However, for time to intervention for a manic episode, lithium separated significantly from placebo, but lamotrigine did not. The opposite effect was seen with time to intervention for depression; while lamotrigine separated significantly from placebo, lithium did not.

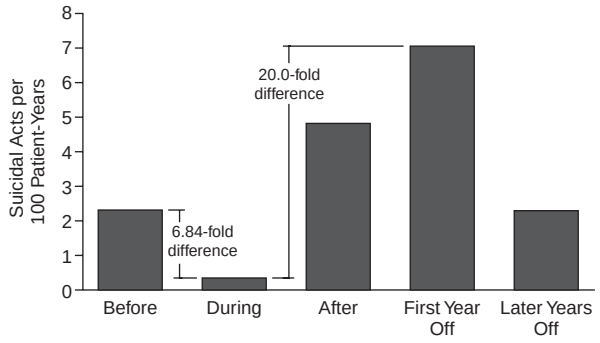
The efficacy of lithium in preventing an episode of mania in patients hospitalized for bipolar disorder was less promising in studies conducted by some tertiary referral academic health centers in the United States in the 1980s. Solomon and colleagues[24] found that, in their study of 33 patients who were hospitalized for 70 episodes of bipolar disorder, lithium treatment did not prevent patients who were experiencing an episode of depression from switching to mania during 14 of the admissions. In a follow-up of 24 patients 4 years after they recovered from their first manic episode and were referred back to the community for care, Tohen and colleagues[25] found that only 46% of patients were stable and that the type of medication, including lithium, was unrelated to patients' outcome. These findings contrast sharply with those outside the United States.

Lithium and Suicide

The ability of lithium treatment to prevent suicides in patients with an affective illness was evaluated in Tondo and colleagues' meta-analysis[26] of 28 studies involving about 17,300 patients. The risk of suicide and suicide attempts was about 3.2 patients per 100 patient-years for those patients not taking lithium but about only 0.37 patients per 100 patient-years for those on lithium treatment. The mean ± yearly risk of suicide or suicide attempts was significantly lower ($p < .0001$) for patients treated with lithium (0.26 ± 0.40) in the 22 studies that provided this rate compared to the risk (1.68 ± 1.50) for those not treated with lithium in the 10 studies that reported this information. In interpreting these huge 7-fold to 8-fold differences, it should be kept in mind that the patients in these studies were not randomly assigned to treatment, so the severity of illness or rates of compliance may have differed between the 2 groups and also influenced the risk of suicide.

Baldessarini and colleagues[27] also studied the risk of suicide attempts before, during, and after treatment with lithium in 310 patients with bipolar disorder in Sardinia, Italy (Figure 1). The number of suicidal acts per 100 patient-years was 0.355 during lithium maintenance treatment—a 6.5-fold reduction from the number before lithium treatment—and 4.86 after lithium discontinuation. The reduction in risk of suicide attempts with lithium maintenance therapy in this Sardinian population was comparable to the reduction in the meta-analysis[26] of 28 studies on suicide risk and lithium. The Sardinian population has been thought to be more responsive to lithium than are other populations, but some of the 28 studies may have also excluded patients, such as those with substance abuse or poor compliance, who may respond poorly to lithium.

Figure 1. Suicide Risk and Lithium Treatment Status[a]



[a]Data from Baldessarini et al.[27]

The most widely replicated biological correlate of suicide is low serotonin function. Therefore, the ability of lithium to reduce suicidal behavior may relate to demonstrations in animal studies of the ion's tendency to enhance and stabilize central serotonin function. There is a dearth of data on the impact of other putative mood stabilizers on suicide risk. Only one randomized clinical trial has compared the suicide risk with lithium or anticonvulsant treatment. Thies-Flechtner et al.[28] studied suicidal acts over 2.5 years in 378 patients randomly assigned to lithium, carbamazepine, or amitriptyline. None of the patients who attempted or completed suicide had taken lithium; the 5 people who attempted suicide and the 9 who completed suicide were taking carbamazepine, amitriptyline, other anticonvulsant or antidepressant drugs, or no medication at the time of their suicidal behavior. Another larger study of suicide in bipolar disorder is now being conducted by my colleagues and me in a health maintenance organization setting, the Kaiser Health System, with about 27,000 patients with bipolar disorder. About one fourth of these patients received long-term lithium monotherapy, one fourth received divalproex, and one fourth received a combination of lithium and divalproex. Data are now being analyzed.

The combination of lithium and another medication may be even more beneficial than treatment with lithium alone. Many clinicians treat patients with a combination of low doses of lithium and anticonvulsants. Studies by Manji, Chen, and colleagues[29,30] suggest that these medications may have shared and specific mechanisms of action that complement one another. Both lithium and divalproex affect the protein kinase C isozymes, the deoxyribonucleic acid binding of activator protein-1 (AP-1) and the expression of both AP-1–regulated genes and the cytoprotective protein bcl-2 in the central nervous system. Lithium also affects hippocampal neurogenesis and increases brain

N-acetyl-aspartate levels and gray matter volume. Divalproex aids the outgrowth of neurites and regulates the mitogen-activated extracellular signal-regulated kinase pathway. This pattern of both similar and dissimilar actions suggests synergism.

CHANGES IN REPORTED LITHIUM RESPONSE OVER THE YEARS

Although many studies conducted outside the United States[12,14,16] have found lithium to be effective in long-term use, some recent studies in the United States[25,31,32] have reported a decline in lithium response rates during long-term treatment. The reasons for this reported decline can be divided into reasons that are related to changes in the course of bipolar disorder and its diagnostic criteria and those that are related to the changes in the nature of lithium studies. As the criteria for this illness have changed, the diagnosis of bipolar disorder has broadened. Under the newer criteria such as the text revision of the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (DSM-IV-TR),[1] there are more psychotic features and increased Axis II comorbidity. In addition, in studies from the 1960s and 1970s, the median age at onset in the United States was about 30 years, but the median age at onset in the United States is now below 20.[5] The comorbidity of substance abuse also increased from about 20% in the 1960s[33] to between 50% and 60% in 1990.[34]

According to most of the literature on lithium, these factors—earlier age at onset with more psychotic features and more substance abuse—would suggest poorer response to lithium monotherapy. Another factor that may explain the reported decline in lithium response rates is the increase in exposure to antidepressants between the 1960s and now. Data show that for patients with bipolar disorder, antidepressants are prescribed more often than mood stabilizers in the United States.[35] This change in prescribing patterns may be a reflection of the number of new antidepressants developed and the extensive marketing they have received in recent years.

The change in the nature of lithium studies has also affected apparent lithium response rates. Current investigators, who have more options than lithium for treating bipolar disorder, may not be as skilled in the use of this medication as were those who conducted earlier studies. Another concern with later studies is that the longer a successful treatment is available in the community, the more difficult it is for research centers to demonstrate efficacy, regardless of the medical specialty. Research centers tend to depend on referrals, so the populations they study tend to include more difficult and treatment-resistant patients than are found in the general population. On the other hand, in Europe, the reverse bias may operate, as specialized lithium clinics get better at selecting patients who respond well to lithium, e.g., those without substance abuse.

To determine whether the general efficacy of lithium had changed, Baldessarini and Tondo[36] used the same system of analysis on data from 360 patients with bipolar disorder who had been treated with lithium for at least 1 year since the 1970s. These researchers analyzed the data by decade and found that about two thirds of patients in the 1970s, 1980s, and 1990s experienced a ≥ 50% reduction in the percentage of time they were ill. Nearly one third also experienced no new episodes during lithium treatment. Further, they examined 24 clinical trials of lithium and found no evidence of a decline in the efficacy of lithium since the 1970s. Although all of these studies were on maintenance treatment with lithium, they had methodological variants. While Baldessarini and Tondo used statistical methods to correct for the variants, no meta-analysis can correct for every variant to ensure the studies are completely comparable.

Another question about lithium is whether it loses its effectiveness in an individual patient over time. To find out whether lithium is as effective during a patient's second trial as during the first, Baldessarini and Tondo[37] conducted a meta-analysis of studies on lithium response. Although it did not definitively settle this issue, this study supports the idea that there is no difference in overall improvement or functioning during a first and second exposure to lithium. The average duration was 4.6 years for the first trial and 4.1 years for the second. The average improvement in time spent ill—in a manic or depressive episode—was 63.5% during the first trial and 54.0% during the second, and this difference was not statistically significant.

Changes in Lithium Prescription Rates

As studies have found different treatments to be effective in bipolar disorder, a shift in prescription patterns has occurred. Fenn and colleagues[38] examined the changes in prescription patterns between 1989 and 1994 for patients with DSM-III-R schizoaffective or bipolar disorder by using a database at the Veterans Affairs Medical Center in Palo Alto, Calif. The use of the combination of lithium and divalproex increased from 0% to 25%. However, the use of the combination of lithium and carbamazepine decreased from 24% to 18%, and the use of lithium monotherapy declined from 84% to 43%. These findings contradict the practice in Europe, where lithium continues to be the most widely used mood stabilizer, followed by carbamazepine and then divalproex.

There are several possible reasons for the decrease in the prescription of lithium in the United States. Because the diagnostic criteria have broadened to include more atypical cases of bipolar disorder and the comorbidity of substance abuse has increased, agents that are more effective than lithium in these cases are often prescribed. Another reason may be related to the practice of continuing antimanic medications as maintenance therapy in the United States, which has been reinforced by managed care

and physicians' decrease in time for each patient. In general, physicians in Europe are taught that decisions about prophylactic treatment should be made separately from decisions about the treatment of acute mania because not all medications are effective in both acute and long-term treatment. A common example is that although haloperidol is an effective treatment for acute mania, this drug would rarely be used as a mood stabilizer. The decrease in the prescription of lithium may also be caused by the decrease in training residents in the United States on how to use lithium, which has led to the perception that lithium is difficult to use and that it has more side effects than do other agents. This relative decrease in education about lithium also relates to the massive imbalance in continuing medical education efforts for lithium compared with divalproex. This in turn is due to the fact that lithium, as a generic drug, generates a smaller gross income than divalproex. Generic formulations of lithium cost patients an average of only $0.50 per day when dosed at 900 mg, whereas divalproex, which has no generic formulations, costs patients an average of $5.50 per day when dosed at 1500 mg. In addition, lithium is prescribed less frequently. For example, Scott-Levin's Physician Drug and Diagnosis Audit shows that in May 2002, 1858 prescriptions for bipolar disorder were for lithium compared with 2116 for divalproex (data on file, Scott-Levin, Newton, Pa., 2002).

DOSAGE AND SIDE EFFECTS OF LITHIUM

The recommended dose of lithium in maintenance therapy is 600 to 900 mg h.s. of immediate-release or sustained-release formulations. Although package inserts and the *Physicians Desk Reference*[39] advise that blood levels of lithium should be between 0.6 and 1.2 mEq/L, current common practice, based on more recent trials, is to maintain lithium blood levels from 0.5 to 0.8 mEq/L. The risk/benefit ratio increases sharply at levels above 0.7 to 0.8 mEq/L. Older patients may be less tolerant of lithium; therefore, their blood drug levels may need to be at the lower end of this range. Adolescents may be more tolerant of lithium than adults and may require a higher dose of lithium to achieve the appropriate blood drug level because their kidneys clear lithium faster than adults' kidneys.[40]

To achieve the optimal effective dose with the fewest side effects, physicians should periodically monitor plasma lithium, and perform yearly creatinine, thyroxine (T_4), and thyroid-stimulating hormone levels. In addition, patients' diet, exercise habits, clinical state, age, medical illnesses, drug use, and pregnancy status should be considered when determining the dosage of lithium. Monitoring for serum drug levels of lithium is indicated because lithium may be toxic at only twice the therapeutic dose. Even if not toxic, high dosages of lithium can be associated with a higher incidence of side effects, which leads to poor compliance.

The 2 most common side effects of lithium were nausea and diarrhea in both the Prien et al.[19] study and the Bowden et al.[41] study of lithium and divalproex. However, these gastrointestinal side effects may occur less frequently in patients taking sustained-release formulations of lithium than in those taking the immediate-release formulations. Patients taking lithium should also be monitored for changes in dermatologic systems and for interactions with drugs such as antipsychotics, thiazide diuretics, nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, xanthines, metronidazole, and calcium channel blockers. Although the risk of Ebstein's anomaly is only 1 in 1500 with lithium, this medication should be used with caution in pregnant patients. Despite these issues, lithium does have medical benefits in addition to reducing the occurrence of bipolar episodes: both its risks and benefits have been far more extensively studied than those of alternative medications, and it costs less than other mood stabilizers, is safer in pregnancy than some anticonvulsants, and reduces the mortality associated with bipolar disorder through suicide prevention.

In the Bowden and colleagues[41] comparison of the side effects of lithium and divalproex, the occurrence of most side effects, such as gastrointestinal illness, weight gain, and tremors, was not significantly different between the 2 drugs. However, polyuria and polydipsia were significantly higher in the lithium-treated group than in the divalproex-treated group, and sedation, infection, and tinnitus were significantly higher in the divalproex-treated group. Because cognitive side effects were not measured, no support was presented for the clinical impression, which may be related to dose, that lithium has more cognitive side effects than does divalproex. Therefore, from these mixed results, one cannot determine whether lithium has more or fewer side effects than does divalproex. The fact that compliance rates for the 2 drugs are comparable suggests that they have similar overall side effect loads. Interestingly, Keck et al.[42] reported that compliance with the combination of modest doses of lithium and divalproex is substantially greater than with either drug alone. This increased compliance might be expected if 2 drugs with different side effect profiles were synergistic in their therapeutic effects.

CONCLUSION

Because of the high risk of recurrence, morbidity, and mortality associated with bipolar disorder, long-term treatment with lithium may be necessary. The only drug approved as maintenance treatment for bipolar disorder by the FDA is lithium, which has extensive evidence of prophylaxis in this illness. Lithium may be somewhat more effective in preventing a manic episode than a depressive episode, but its substantial reduction in suicide suggests efficacy in depression as well. However, some patients, especially those with nonclassical features of bipolar disorder,

may respond better to other agents, either alone or in combination with lithium or another medication. Therefore, there is a need for more research comparing the effectiveness of lithium and other agents in reducing the symptoms and risk of death associated with bipolar disorder. To ensure that each patient receives the most tolerable and effective treatment, physicians must educate their patients about the need and options for long-term treatment for bipolar disorder.

Drug names: amitriptyline (Elavil, Endep, and others), carbamazepine (Epitol, Tegretol, and others), divalproex (Depakote), haloperidol (Haldol and others), lamotrigine (Lamictal), metronidazole (Flagyl, Noritate, and others), olanzapine (Zyprexa).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, carbamazepine, divalproex, lamotrigine, metronidazole, olanzapine, and oxcarbazepine are not approved by the U.S. Food and Drug Administration for the maintenance treatment of bipolar disorder.

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