Long-Term Treatment of Bipolar Disorder With Lamotrigine

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Bipolar depression is as debilitating as mania in bipolar disorder, but the treatment of bipolar depression has historically received less attention. To date, there is no mood stabilizer (liberally defined as a medication that decreases episode severity, duration, or frequency in one phase of bipolar illness without producing a negative effect in other phases) that demonstrates similar efficacy in both the depressive and the manic phases of bipolar disorder. However, bipolar depression—which is prevalent, sometimes chronic, and associated with a low quality of life and a high risk of suicide—must be addressed as energetically as mania. Recent research into the long-term treatment of bipolar disorder has raised several questions about the generalizability of early lithium studies, as a result of these studies' designs. Researchers conducting more recent studies of mood stabilizers in the long-term treatment of bipolar disorder have attempted to clarify their results by, for example, performing survival analyses of the data. Until pharmacotherapy has been found that is equally efficacious in the treatment of both manic and depressive episodes in bipolar disorder, the use of combination therapy to manage bipolar disorder is advised. Lithium and divalproex sodium remain the first-line treatments for mania. Lamotrigine has been found to have acute efficacy in treating episodes of bipolar depression without increasing cycling or provoking a switch into mania, as well as a long-term role in delaying relapse and recurrence of depressive episodes.
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Bipolar disorder is a lifelong illness for which there are currently few comprehensive treatment options. Promising possibilities in the treatment of bipolar disorder such as anticonvulsants and atypical antipsychotics have largely been investigated first as potential treatments for mania,[1] while research into the treatment of bipolar depression remains relatively neglected.[2] However, the depressive episodes of bipolar disorder can be recurrent and debilitating, especially in patients with a high rate of episode frequency, or rapid cycling. In these patients, depressive episodes may occur 2 to 3 times more often than hypomanic episodes.[3] Further, in patients with rapid cycling, depressive episodes may be more treatment refractory than episodes of hypomania or mania.[4] The depressive phase of bipolar disorder is chronic in 20% of patients[5] and is associated with a self-reported lower quality of life.[6] In addition, bipolar depression is associated with considerable morbidity and a striking mortality rate. According to the DSM-IV,[7] 10% to 15% of individuals with bipolar disorder die by suicide.

In line with this statistic, Bowden et al.[8] pointed out that long-term outcomes in bipolar disorder are often poor despite currently available treatment. Nevertheless, maintenance treatment is at the heart of managing a lifelong disorder. Consequently, options for the long-term management of patients with bipolar disorder must move beyond the treatment of acute mania to encompass the full scope of the illness, including depression, hypomania, and subsyndromal symptoms too.[1] Although mania is sometimes the most apparent and dramatic expression of bipolar disorder, frequently resulting in hospitalization or other emergency measures, the depressive phases of the illness must not be overshadowed. The successful management of bipolar disorder requires a mood stabilizer with a broad spectrum of efficacy. If monotherapy proves impossible or impractical, mood stabilization must be achieved through the use of agents that possess complementary spectra of efficacy.[1]

WHAT IS A MOOD STABILIZER?

The definition of a pharmacologic mood stabilizer is at present nascent and disputable. Ketter and Calabrese[1] report 2 functional definitions for the purposes of bipolar disorder. A mood stabilizer is a medication that shows

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direct efficacy in decreasing the manic episode's severity, duration, or frequency "from above baseline"[1] (baseline being normal mood) without exacerbating the depressive phase, or it is a medication that decreases the depressive episode's severity, duration, or frequency "from below baseline" without destabilizing the course of the illness by producing a negative effect on the manic phase. Treatments that exemplify the first include lithium, divalproex, carbamazepine, and the atypical antipsychotics. As the only illustration of the second, the anticonvulsant lamotrigine emerges as the prototype of this new class of mood stabilizers. There are older data[9,10] that suggest that lithium has efficacy in the treatment of the depressed phase of the illness, but these findings have not been replicated using contemporary maintenance study methodology (i.e., survival analytic techniques). Of these pharmacotherapies, lithium is considered the gold standard for first-line acute and maintenance treatment of bipolar disorder. It is the best known and the most extensively studied of mood stabilizers. However, many of the data regarding the prophylactic efficacy of lithium in maintenance treatment prove difficult to interpret as a result of study design.

METHODOLOGY OF OLDER LITHIUM STUDIES AND THE ROLE OF SURVIVAL ANALYSIS

The last 2 positive placebo-controlled lithium maintenance studies in the treatment of bipolar I disorder were published in 1973[11] and 1974[9] by Prien et al. The combined results of these studies showed a significantly lower incidence of mania and depression in lithium-treated patients. However, the maintenance study published by Prien and colleagues in 1984[10] (and its reanalysis by Shapiro et al.[12] in 1989) did not replicate these findings. Studies of lithium[11,13–16] completed in the 1970s, at a time when lithium was indeed a revolutionary drug, tended to support lithium's efficacy in preventing both mania and (to some extent) depression in bipolar disorder. More recent evaluations[8,17] of these early lithium prophylaxis studies have found design weaknesses that temper the studies' results and conclusions.

The methodology of prior lithium studies relied upon comparison of the percentages of patients who experienced relapse, usually defined as a return of symptoms that requires additional rehospitalization or additional pharmacotherapy. Thus, there are no maintenance studies in bipolar disorder that have been designed to show true prophylaxis, which is the prevention of a new mood episode. Instead, previous lithium studies have shown the maintenance of the acute and continuation effect: the prevention of the recurrence of the recent episode. A true prophylaxis study would require the absence of relapse when patients were not taking the medication following acute and continuation care, prior to randomization, in order to demonstrate prophylactic efficacy.

Additionally, many early lithium maintenance studies did not use established diagnostic criteria to limit their samples to only those patients with bipolar depression. For example, some included individuals with unipolar major depressive disorder. Many such studies also did not employ random assignment to parallel groups but used instead lithium/placebo crossover designs that may have confounded the interpretation of lithium's antidepressant performance. Furthermore, these early studies often neglected outcome measures and relied on the analysis of observed data rather than employing last-observation-carried-forward (LOCF) analysis. Many early lithium maintenance studies also deleted noncompleter data without analyzing reasons for dropout.[8,17]

In fact, the use of survival analysis is a new analytic technique in the methodology of placebo-controlled lithium maintenance studies. It is a time-to-event analysis. As the name suggests, survival analysis was originally used in studies of terminal disease in which the endpoint event was death. In a study of mood disorders using survival analysis, the endpoint event is generally relapse or intervention with an additional treatment for emerging symptoms. Long-term studies increasingly employ survival analyses because these analyses provide novel information in longitudinal studies. For example, if all patients in a study experience a relapse, but the group receiving treatment A experiences relapse many months later than the group receiving treatment B, then survival analysis indicates the superior efficacy of treatment A. Longer survival in the study is associated with a better treatment outcome. Survival analysis also helps to identify the point at which patients would benefit from a change of treatment and the point at which patients stop adhering to a treatment regimen.

RECENT STUDIES OF TREATMENTS FOR BIPOLAR DISORDER

Although the treatment focus in bipolar disorder has been on the manic phase, depressive symptoms are often more persistent and debilitating. Lithium appears to be less effective in treating depression than it is in treating mania, and more studies are needed to determine a safe and effective treatment for patients in the depressed phase. There is some concern that antidepressants are overutilized in the treatment of bipolar disorder.[18] Patients with bipolar disorder commonly receive antidepressants as a therapy adjunctive to lithium or anticonvulsants. Yet antidepressants have not been proved effective in this role[19] and may actually put patients at an increased risk for switching into mania or hypomania.[1] The need for treatments that would have long-term prophylactic efficacy has inspired recent research into new medications for the treatment of bipolar disorder.

In 2000, Bowden et al.[8] published the first placebo-controlled bipolar disorder maintenance study in 20 years. The study was also the first randomized, blinded, parallel-group comparison of divalproex with lithium and placebo in the prophylactic treatment of bipolar disorder, and it employed survival analysis. Patients experiencing a remission of bipolar disorder were randomly assigned to divalproex, lithium, or placebo treatment and then monitored for 52 weeks. The primary outcome measure was time to any mood episode (manic or depressive).

Results showed no significant differences between lithium and divalproex by the primary outcome measure, although divalproex was slightly favored over lithium. However, differences were evident by secondary measures. Importantly, patients receiving divalproex were less likely to prematurely terminate treatment than those receiving lithium or placebo. Patients in the lithium group had significantly higher termination rates resulting from study drug intolerance and noncompliance than those in the placebo group. Patients in the divalproex group showed a significantly lower rate of termination due to recurrent mania or depression than those in the placebo group, and they were significantly less likely to be dropped from the study due to depressive episodes. Altogether, patients receiving divalproex remained in treatment significantly longer than those treated with lithium.[8]

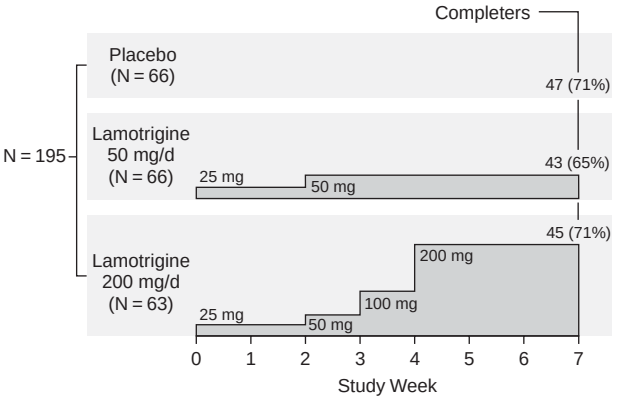
These data support the effectiveness of divalproex and may explain recent reports of poor adherence to treatment regimens including lithium. Ketter and Calabrese[1] have emphasized that patients tend to discontinue lithium maintenance treatment outside of controlled studies, perhaps due to a less vigilant level of follow-up, inconveniences such as the need to monitor serum level and renal function, or adverse side effects such as weight gain.

LAMOTRIGINE IN THE TREATMENT OF BIPOLAR DEPRESSION

Lamotrigine has also been explored in the treatment of bipolar depression, with promising results. During its development as an anticonvulsant agent, lamotrigine was observed to improve mood, alertness, and sociability in trial subjects.[20] Recently, Calabrese et al.[17] studied lamotrigine in the first randomized, placebo-controlled, parallel-group trial to test any monotherapy for bipolar I disorder depression.

In the short-term phase of this study,[17] 195 patients with bipolar I disorder, currently experiencing a depressive episode, were randomly assigned to a dose of 200 mg/day of lamotrigine, 50 mg/day of lamotrigine, or placebo. Patients were assessed at a screening visit, at a baseline visit, on the fourth day of treatment, and at the end of every week for the 7-week duration of treatment. Assessment tools were the Hamilton Rating Scale for Depression (HAM-D), the Montgomery-Asberg Depression Rating Scale (MADRS), the Mania Rating Scale (MRS), and the Clinical Global Impressions scale for Severity of Illness (CGI-S) and Improvement (CGI-I).

Figure 1. Lamotrigine in Bipolar Depression[a]



[a]Adapted with permission from Calabrese et al.[17]

All patients who continued through at least 1 post-randomization assessment were included in the efficacy analyses.[17] In addition to the analysis of observed data at each timepoint, efficacy variables were assessed using LOCF scores. All patients who received at least 1 dose of the study drug were included in the compliance and the safety analyses. Approximately 30% of the patients entering the study did not complete it, owing to adverse events, inadequate response, protocol violation, or other reasons (Figure 1). These noncompleting patients almost equally represented all treatment groups.

Switching into a new mood episode occurred in 8% of patients assigned to 200 mg/day of lamotrigine, in 5% of patients assigned to placebo, and in 3% of patients assigned to 50 mg/day of lamotrigine.[17] Ninety-two percent of patients in the placebo group reported an adverse event versus 79% of patients in each lamotrigine group. Headache was the most commonly reported adverse side effect, as well as the only one to be reported more often by lamotrigine-group patients than by placebo-group patients. Rash was reported by 11% to 14% of patients in each of the 3 treatment groups. No incidence of rash was considered serious or required hospitalization. This finding is supported by a review of data on the incidence of rash in lamotrigine trials (Table 1).[21]

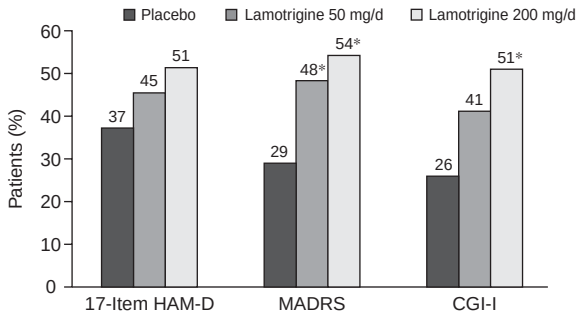
Calabrese et al.[17] concluded from the results of this short-term study that lamotrigine had significant antidepressant efficacy in bipolar I depression, although the frequency of any mood episode did not differ significantly between either of the lamotrigine groups and placebo. Lamotrigine appeared to ameliorate bipolar depression as early as the third week of treatment. At the 200-mg dosage, lamotrigine evoked a rate of improvement almost twice as high as that of placebo (Figure 2). The

Table 1. Rash in Placebo-Controlled and Open-Label Mood Disorder Trials of Lamotrigine[a]

Condition	N	Benign	Serious[b]	SJS/TEN
All exposures				
Lamotrigine	3153	12.0% (366)	2 (< 0.1%)[c]	0
All placebo-controlled exposures				
Lamotrigine	1198	9.0% (108)	0	0
Placebo	1056	7.6% (80)	1 (< 0.1%)	0
Comparators[d]	427	6.1% (26)	0	0

[a]Calabrese et al., unpublished data. Abbreviations: SJS = Stevens-Johnson syndrome, TEN = toxic epidermal necrolysis.
[b]Requiring discontinuation and hospitalization.
[c]This is a conservative estimate of open-label, non-duplicated patient exposures. Benign rash rates are presently unavailable. Serious rash rates are based on 2 confirmed cases of serious rashes during open-label trials.
[d]Lithium (N = 280) or desipramine (N = 147).

Figure 2. Lamotrigine vs. Placebo in Bipolar Depression: Marked Response[a]



[a]Adapted with permission from Calabrese et al.[17]
Abbreviations: CGI-I = Clinical Global Impressions-Improvement, HAM-D = Hamilton Rating Scale for Depression, MADRS = Mongomery-Asberg Depression Rating Scale.
*p < .05 vs. placebo.

200-mg/day dose of lamotrigine compared with the 50-mg/day dose of lamotrigine demonstrated increased efficacy without increased side effects. The 50-mg dose of lamotrigine showed intermediate efficacy. These data are consistent with the findings of earlier uncontrolled clinical reports of Lamotrigine's efficacy in bipolar depression,[20,22–25] which have asserted lamotrigine's acute and prophylactic antidepressant efficacy in bipolar I disorder and its prophylactic antidepressant efficacy in rapid-cycling bipolar II disorder.

Those patients who completed the 7-week study by Calabrese et al. were then asked to participate in a 1-year continuation study of lamotrigine. Preliminary results were presented at the 2001 meeting of the American Psychiatric Association (Lamotrigine 605[26] and 606[27]). The Lamotrigine 606 study used a double-blind, placebo-controlled, flexible-dose design and employed survival analysis. This study compared the prophylactic efficacy of lamotrigine with that of lithium and placebo over 18 months, among 175 stabilized patients with bipolar disorder who had recently experienced a manic episode. The primary outcome measure was time to intervention for any mood episode. Secondary outcome measures were overall survival (time to study discontinuation on the part of the patient for any reason), time to intervention for symptoms of mania or depression, and changes in patients' scores on the MRS, HAM-D, CGI-S, and Global Assessment Scale. Results indicated that both lamotrigine and lithium were effective in long-term mood stabilization.

CONCLUSION

At present, there is no mood stabilizer that possesses a similar degree of efficacy in treating both the manic and the depressive phases of bipolar disorder.[1] Still, the dichotomous, cycling nature of bipolar disorder requires a therapeutic plan that treats both debilitating phases of the illness, without neglecting or exacerbating one phase for the sake of managing the other. Likewise, the disorder's longevity requires long-term, maintenance treatment. Thus, long-term treatment of bipolar disorder requires that a drug or combination of drugs shows safety and efficacy in treating and preventing both manic (or hypomanic) and depressive episodes.

Antidepressants should be avoided, if possible, in the treatment of bipolar disorder, but clinicians should move quickly to some form of combination therapy if monotherapy is not successful. Moving forward with research into the treatment of bipolar depression will require more data gathered in studies whose designs allow extrapolation and interpretation of results. In the meantime, clinicians may be advised to use combination therapy (such as divalproex, lithium, or an atypical antipsychotic to treat mania, and lamotrigine to treat bipolar depression) in the long-term treatment of patients with bipolar disorder.

Drug names: carbamazepine (Tegretol and others), divalproex (Depakote), lamotrigine (Lamictal).

Disclosure of off-label usage: The authors of this article have determined that, to the best of their knowledge, lamotrigine is not approved by the U.S. Food and Drug Administration for the treatment of bipolar disorder.

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