A 52-Week, Open-Label Continuation Study of Lamotrigine in the Treatment of Bipolar Depression

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Background: Lamotrigine has demonstrated efficacy for the acute treatment of depression in bipolar I patients in a placebo-controlled, monotherapy study. We describe the results of a 52-week, open-label continuation of that trial.

Method: Patients meeting DSM-IV criteria for bipolar I disorder with a current major depressive episode who completed a 7-week, double-blind study of bipolar depression were offered 1 year of open-label lamotrigine therapy (flexible doses of 100–500 mg/day) in a continuation study. To maintain the acute study blind, the first 3 weeks of the continuation study remained blinded while patients previously randomly assigned to placebo were titrated to a lamotrigine dose of 50 mg/day. Patients who had been randomly assigned to lamotrigine continued at their fixed doses. Beginning at week 4, all patients received open-label lamotrigine for up to 49 additional weeks. Concomitant psychotropic medications were permitted during the open-label phase. Effectiveness (Montgomery-Asberg Depression Rating Scale [MADRS], Clinical Global Impressions-Improvement scale) and safety assessments were administered at weeks 4, 12, 24, 36, and 52. The study was conducted from June 1996 to December 1998.

Results: Of 135 patients completing the acute study, 124 (92%) entered the continuation study: 77 had received lamotrigine and 47 had received placebo in the acute study. The mean duration of lamotrigine exposure was 10.4 months, with a mean modal dose of 187 mg/day. Sixty-nine patients (56%) completed 1 year of treatment. Significant and sustained improvement from baseline was seen in mean observed MADRS scores ($p < .05$). The proportion of patients achieving remission (MADRS score ≤ 11) by week 4 of the study was 81.4%, and episodes of mania/hypomania occurred less frequently than in the preceding year. Headache was the most common drug-related adverse event.

Conclusion: During 1 year of open-label therapy with lamotrigine as adjunctive therapy or monotherapy, bipolar I patients experienced sustained improvement in depressive symptoms without evidence of mood destabilization.

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Bipolar I disorder is a chronic psychiatric disorder that causes potentially lifelong impairment. Approximately 1.2% to 1.6% of the adult population in the United States suffers from bipolar I disorder,[1,2] with the broader bipolar spectrum appearing at least twice as prevalent in recent estimates as previously reported.[3] The estimated annual U.S. cost of bipolar disorder was $45 billion in 1990, more than the $40 billion spent on depression and exceeded only by the $64 billion spent on schizophrenia.[4] Compared with symptoms of mania, depressive symptoms predominate in bipolar I disorder.[5] The length of time an average bipolar I patient experiences depressive symptoms is nearly 3 times as long as the time spent experiencing manic symptoms, and depression is the most common reason given for seeking medical treatment.[5] Bipolar depression has also been associated with poor psychosocial functioning and a greater risk of suicide compared with mania.[6]

The burden of illness caused by bipolar depression is extensive. Bipolar depression occurs more frequently than mania, is longer lasting, and is particularly difficult to treat.[5] Despite the substantial burden of illness caused by depressive symptoms,[7] bipolar depression remains remarkably understudied. Treatments effective for acute mania and maintenance therapy are not as effective for depressive symptoms or have not been adequately studied in this phase of the illness.[8,9] The addition of a standard antidepressant to a mood stabilizer may lessen depressive symptoms over the short term; however, antidepressants do not maintain bipolar depressive remission as effectively as the remission from mania brought about by mood

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stabilizers such as lithium.[10] Further, antidepressant monotherapy may precipitate mood instability and even mania and thereby worsen the course of bipolar disorder.[11–13]

Lamotrigine is a novel antiepileptic drug that blocks sodium channels to stabilize the neuronal membrane and inhibit the release of the excitatory amino acids (e.g., glutamate) associated with seizure activity.[14,15] A 7-week, double-blind, placebo-controlled study demonstrated that lamotrigine monotherapy was effective for the treatment of acute depressive episodes in 159 patients with bipolar I disorder as early as 3 weeks after initiation of therapy.[16] More recently, the tolerability and efficacy of lamotrigine monotherapy in delaying intervention for depressive mood episodes in bipolar I disorder were established in 2 pivotal 18-month placebo-controlled maintenance studies[17,18] and a meta-analysis of those 2 trials in which lamotrigine was found to significantly reduce mean Hamilton Rating Scale for Depression (HAM-D)[19,20] and Clinical Global Impressions-Severity of Illness (CGI-S) scores across 76 weeks of treatment in 638 patients.[21]

Although the results of these placebo-controlled clinical trials are encouraging, their relationship to actual clinical practice was limited by a research design that required patients to have attained some degree of mood stability (CGI-S score of ≤ 3 for 4 continuous weeks) during lamotrigine monotherapy. Therefore, we conducted a 1-year open-label continuation study (protocol SCAB2002, 106-604) following the 7-week acute study[16] to evaluate the long-term effectiveness and tolerability of lamotrigine for treatment of bipolar I depression in a more naturalistic patient care setting where adjunctive psychotropic therapy was permitted.

METHOD

Patients

Adults 18 years or older entered the 52-week continuation study immediately following completion of the 7-week acute study described elsewhere.[16] In brief, at entry into the acute study, patients were required to have a DSM-IV diagnosis of bipolar I disorder with a current major depressive episode (HAM-D-17 score ≥ 18) of at least 2 weeks but not greater than 1 year in duration. Patients were also required to have had at least 2 mood episodes during the previous 10 years, at least 1 of which must have been a manic or mixed episode. Patients could not have a DSM-IV diagnosis of or have received treatment for panic disorder, obsessive-compulsive disorder, social phobia, bulimia nervosa, or rapid cycling in the 12 months prior to study entry. Patients could not have thyroid abnormalities or a history of lamotrigine use prior to the acute study; be pregnant, lactating, or at risk of becoming pregnant; or have had substance (alcohol or drug) dependence in the past year or substance abuse within 4 weeks prior to study entry.

To enter the present study, patients had to complete the 7-week acute study and express desire to pursue treatment with open-label lamotrigine. All patients provided written informed consent prior to participating in the continuation study, and the institutional review boards of each clinical site approved the protocol. The study was conducted from June 1996 to December 1998.

Procedure

The continuation study was conducted in 2 phases, a 3-week double-blind phase to protect the blinded treatment assignment from the preceding acute study, followed by a 49-week open-label phase. Double-blind treatment consisted of either (1) dose escalation of lamotrigine (25 mg/day for 2 weeks followed by 50 mg/day for 1 week, for patients assigned to placebo in the acute study) or (2) continuation of lamotrigine at acute study dosing (50 or 200 mg/day). Following the double-blind phase, open-label dosing commenced at 100 mg/day for all patients. The dosage could subsequently be adjusted by the investigator to improve effectiveness or tolerability within a range of 100 to 500 mg/day in maximum increments of 100 mg/week.

Concomitant psychotropic medications were not allowed during the initial 3-week double-blind phase of the continuation study, with the exception of chloral hydrate and benzodiazepines prescribed as needed for agitation, irritability, restlessness, insomnia, and hostile behaviors. However, no restrictions were placed on the use of concomitant psychotropic medications during the open-label phase. Drugs that could confound psychiatric assessments could not be taken during the 8 hours prior to the administration of the psychiatric rating scales. Lamotrigine dosage was adjusted for concomitant valproate or carbamazepine treatment.[22]

Effectiveness, safety, and tolerability were assessed at visits scheduled for weeks 4, 12, 24, 36, and 52 or study termination, or as needed to address patient safety or clinical state.

Assessments

Depressive symptoms were assessed using the Montgomery-Asberg Depression Rating Scale (MADRS),[23] and illness severity was assessed with the Clinical Global Impressions-Improvement scale (CGI-I).[24] Safety was assessed by adverse event reporting at all visits and by clinical laboratory assessments (hematology, blood chemistries, and urine pregnancy tests for women of childbearing age) at weeks 12, 24, 36, and 52 and urinalysis at screening and week 52. Investigators were instructed to report manic, hypomanic, and mixed episodes as adverse events. A follow-up visit was conducted within 14 days of study termination to record adverse events and concomitant medication use and to complete the final psychiatric review.

Statistical Analysis

The effectiveness population was composed of all patients who received at least 1 dose of study drug and had at least 1 effectiveness evaluation. All patients who received at least 1 dose of study drug were evaluated for safety. Two descriptive analyses were performed on each effectiveness parameter. First, a summary by randomized treatment group from the acute study was produced from screening of the acute study, end of the acute study, and weeks 4, 12, 24, 36, and 52 or study termination of continuation study. Second, the mean changes in psychiatric rating scale scores from the first time of exposure to lamotrigine were summarized according to total weeks of lamotrigine treatment (i.e., combined exposure during the acute and open-label studies). Last-observation-carried-forward methodology was used to account for any missing data points. To evaluate the effect of time on the effectiveness of lamotrigine, the change in MADRS score from screening in the acute study was analyzed in a repeated-measures analysis of variance. Patients with MADRS scores ≤ 11 were considered to have experienced remission. Kaplan-Meier methodology was used to estimate the cumulative probability of remission by time.

Clinical chemistry and hematology data were evaluated using descriptive statistics and median change from screening in the acute study, and 2-sided 95% confidence intervals based on the Wilcoxon signed rank test were computed at each postscreening (acute study) timepoint.

RESULTS

Patients

Of 135 patients completing the acute study, 124 patients (92%) entered the continuation study. Table 1 presents patient demographics and illness characteristics. The majority of patients were white and female, with a mean age of 41 years. In the year prior to enrolling in the acute study, over 60% of patients reported some form of manic, hypomanic, or mixed episode and 100% of patients reported a depressive episode, a requirement for inclusion in the acute study. Mean MADRS scores (placebo = 28.5, lamotrigine = 28.3) at screening in the acute study were consistent with moderate-to-severe depression.

Seventy-seven patients (62%) in the continuation study had received lamotrigine in the acute study and 47 patients (38%) had received placebo. Sixty-nine patients (56%) completed the 52-week study; 55 patients (44%) withdrew for various reasons that included adverse events (N = 18, 14%, of which N = 4, 3% were for mania), lack of effectiveness of treatment (N = 9, 7%), lost to follow-up (N = 12, 10%), and other (N = 16, 13%). At the end of the acute study, patients who had been treated with placebo had higher mean MADRS scores (placebo = 18.5, lamotrigine = 12.2) and CGI-I scores (placebo = 3.0, lamotrigine = 2.3) compared with lamotrigine-treated patients.

Table 1. Patient Demographics and Characteristics (N = 124) From a 1-Year Open-Label Continuation Study of Lamotrigine for Treatment of Bipolar I Disorder[a]

Characteristic	Value
Age, mean, y	41.4
Female	75 (60)
Ethnicity	
White	116 (94)
Black	6 (5)
Other	2 (2)
Family history of bipolar disorder	33 (27)
Family history of major depression	56 (45)
Prior psychiatric hospitalization	61 (49)
History of prior suicide attempt	31 (25)
Age at onset of bipolar symptoms, mean (range), y	20.3 (5–68)
No. of mood episodes in previous 12 mo	
Mania	
1	46 (37)
2	8 (7)
Hypomania	
1	23 (19)
Depression	
1	88 (71)
2	34 (27)
3	2 (2)
Mixed	
1	7 (6)
2	1 (< 1)

[a]Values shown as N (%) unless otherwise specified.

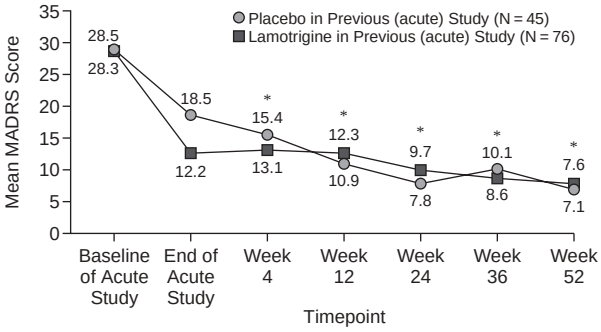
Treatment Response

Montgomery-Asberg Depression Rating Scale. Figure 1 displays observed mean MADRS scores from screening in the acute study through 52 weeks of open-label treatment. Patients who were previously randomly assigned to placebo and received lamotrigine for the first time in the continuation study showed significant improvement in MADRS scores ($p < .05$) as early as week 4 and at weeks 12, 24, 36, 52, and study termination, with a maximum mean decrease of 9.7 points at week 52. Throughout 52 weeks of treatment, patients who received lamotrigine in the acute study maintained the improvements in MADRS scores reported at the end of that study. No statistically significant differences were observed between groups at any timepoint.

Considering the total exposure to lamotrigine for both treatment groups, mean MADRS scores decreased significantly from the first dose of lamotrigine in the acute and the open-label studies at 12 (–16.4), 24 (–18.1), 36 (–18.2), and 52 (–19.8) weeks of lamotrigine exposure and at study termination (–17.0). A repeated-measures analysis indicated a consistent response to treatment with lamotrigine from week 12 through week 52 (time effect $p = .316$).

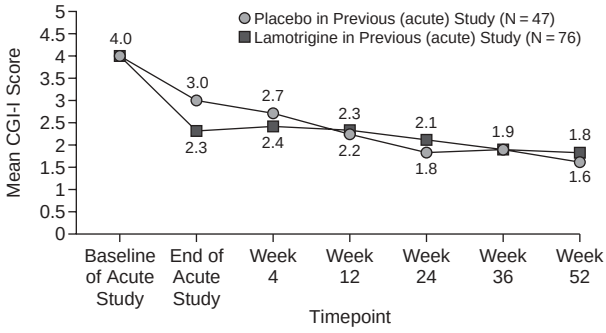
Clinical Global Impressions-Improvement scale. Figure 2 displays CGI-I scores from screening in the acute study through 52 weeks of open-label treatment. Global impressions of improvement were similar between treatment groups and remained stable throughout 52 weeks of

Figure 1. Montgomery-Asberg Depression Rating Scale (MADRS) Scores From Acute Study Baseline to Week 52, by Acute Study Treatment Group, Among Bipolar Disorder Patients Receiving Open-Label Continuation Treatment With Lamotrigine (efficacy population)[a]



[a]Mean changes from baseline in MADRS scores were statistically significant at weeks 4, 12, 24, 36, and 52 for the group who had previously received placebo. Patients who received lamotrigine in the acute study experienced sustained improvement in depressive symptoms. No significant differences in mean MADRS scores were observed between patients who received placebo and those who received lamotrigine in the acute study. Ns for the placebo group differ from those used in the CGI-I analysis due to missing data.
*$p < .05$ vs. baseline for patients who received placebo in the previous study.

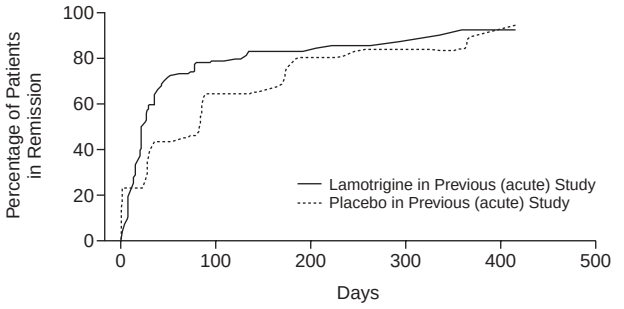
Figure 2. Clinical Global Impressions-Improvement (CGI-I) Scores From Acute Study Baseline to Week 52, by Acute Study Treatment Group, Among Bipolar Disorder Patients Receiving Open-Label Continuation Treatment With Lamotrigine



open-label treatment. Considering the total exposure to lamotrigine for both treatment groups, mean CGI-I scores showed improvement from baseline at week 12 (2.3), week 24 (2.0), week 36 (2.0), week 52 (1.8), and study termination (2.3).

Remission. Figure 3 presents the time to remission of depression (MADRS score ≤ 11) for patients who had previously received either placebo or lamotrigine in the acute study. The overall median time to remission (MADRS) from the start of lamotrigine treatment was 4 weeks; 81.4% (101/124) of the patients achieved remission by week 4.

Figure 3. Time to Remission (MADRS score ≤ 11) for Bipolar Disorder Patients in a 52-Week Open-Label Lamotrigine Trial Who Had Received Placebo or Lamotrigine in a Previous Acute Study



Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale.

Mood stability. In the year prior to entry into the acute study, 62% of patients reported experiencing a manic, hypomanic, or mixed episode. After 52 weeks of lamotrigine therapy, 38 patients (31%) reported some form of manic episode: 7 patients (6%) reported mania, 23 (19%) reported hypomania, and 10 (8%) reported a mixed episode (patients could report more than 1 category of mania). Of the patients who reported manic, hypomanic, or mixed episodes in the continuation study, 24 (63%) had reported some form of manic episode in the 12 months prior to entry into the acute study.

Concomitant medications. Overall, 96/124 patients (77%) used some form of concomitant medication during the continuation study, and 64 (52%) of these patients used psychotropic medications. Table 2 summarizes concomitant psychotropic medications. The prevalence of additional therapy with mood stabilizers (lithium, valproate, or carbamazepine, 13%) was low during the study, and even fewer patients (7%) received antipsychotics. Nearly one third of patients reported using antidepressants. Of the patients who reported some type of manic episode in the continuation study, 12 (32%) used antidepressants during the study, and 8 (21%) used antidepressants within 1 month of the manic episode. Another one third of the patients used concomitant benzodiazepines.

The most commonly used nonpsychotropic medications were nonsteroidal anti-inflammatory drugs (32%), other analgesics (acetaminophen, 22%), salicylates (19%), antihistamines (H_1 antagonists, 19%), and corticosteroids (15%).

Safety and Tolerability

Extent of exposure. Forty-eight percent of patients received lamotrigine as monotherapy. Sixty-eight patients (55%) were exposed to at least 48 weeks of lamotrigine therapy, 60 patients (48%) were exposed to 52 weeks of lamotrigine therapy, and 53 patients (43%) were exposed

Table 2. Summary of Concomitant Psychotropic Medication Use (safety population)

Concomitant Medication	N (%)
Any psychotropic medication	64 (52)
Antidepressants	39 (31)
Atypical antidepressants[a]	14 (11)
SSRIs	13 (10)
Other antidepressants[b]	9 (7)
Tricyclic antidepressants	2 (2)
MAOIs	1 (< 1)
Lithium	12 (10)
Anticonvulsants	7 (6)
Valproate	4 (3)
Carbamazepine	1 (< 1)
Gabapentin	1 (< 1)
Primidone	1 (< 1)
Antipsychotics	9 (7)
Olanzapine	3 (2)
Risperidone	3 (2)
Perphenazine	2 (2)
Chlorpromazine	1 (< 1)
Miscellaneous	
Benzodiazepines	38 (31)
Other anxiolytics, sedatives, and hypnotics[c]	12 (10)

[a]Bupropion (N = 9, 7%), nefazodone (N = 5, 4%), trazodone (N = 3, 2%).
[b]Mirtazapine (N = 4, 3%), hypericum (N = 3, 2%), venlafaxine (N = 2, 2%).
[c]Zolpidem (N = 12, 10%).
Abbreviations: MAOI = monoamine oxidase inhibitor, SSRI = selective serotonin reuptake inhibitor.

Table 3. A Summary of Drug-Related Adverse Events (≥ 5%) From a 52-Week Open-Label Continuation Study of Lamotrigine for Treatment of Bipolar I Disorder

Adverse Event	N (%)
Drug-related adverse event (any)	97 (78)
Headache	36 (29)
Hypomania[a]	15 (12)
Mixed episodes	9 (7)
Mania[a]	2 (2)
Somnolence	14 (11)
Diarrhea	12 (10)
Nausea	12 (10)
Rash	11 (9)
Dizziness	9 (7)
Xerostomia	9 (7)
Amnesia	8 (6)
Pain	8 (6)
Vomiting	7 (6)
Blurred vision	7 (6)
Constipation	6 (5)
Tremor(s)	6 (5)
Accidental injury	6 (5)
Insomnia	6 (5)

[a]Investigator-determined.

to more than 52 weeks of therapy. The mean length of lamotrigine treatment was 10.4 months, with mean average and modal total daily lamotrigine doses of 165.5 and 186.6 mg/day, respectively.

Adverse events. Overall, 115 patients (93%) reported a treatment-emergent adverse event. Of these, 97 patients (78%) reported an adverse event that was considered by an investigator to be reasonably attributable to lamotrigine (Table 3). Headache was the most common drug-related adverse event. No cases of serious rash were reported. There were no deaths during the study.

The most common adverse event leading to study withdrawal was nonserious rash (N = 6, 5%). Seven patients (6%) withdrew from the study due to serious adverse events, which included attempted suicide (N = 2, 2%), suicidal ideation (N = 2, 2%), and mania (N = 4, 3%) (patients could report more than 1 category). The 2 suicide attempts occurred after 12 weeks of lamotrigine exposure. None of these events were attributed to use of lamotrigine.

DISCUSSION

In this open-label continuation study, lamotrigine significantly improved bipolar depression symptoms in lamotrigine-naive patients (N = 47) and maintained previous therapeutic gains in patients who had received acute treatment with lamotrigine across an average of 10 months of treatment. Significant improvements in psychiatric rating scale scores of depression were observed after only 4 weeks of treatment at below-target doses. Half the patients in the study received concomitant psychotropic medications. Surprisingly, few patients received additional treatment with lithium (10%), valproate (3%), or carbamazepine (< 1%), while nearly a third of patients received benzodiazepines and another third received antidepressants. Importantly, lamotrigine was well tolerated as both monotherapy and adjunctive therapy at mean doses less than 200 mg/day, with no cases of serious rash. Taken together with the results of the preceding 7-week acute study[16] and the 2 double-blind, placebo-controlled 18-month maintenance studies,[17,18] these results suggest that lamotrigine is effective for the acute and long-term management of bipolar I depression.

In addition to reducing depressive symptoms, lamotrigine maintenance therapy may have also reduced mood instability during the study. In the year prior to entry into the acute study, more than 60% of patients reported experiencing a manic, hypomanic, or mixed mood episode. After 52 weeks of lamotrigine therapy, less than one third of all patients reported some form of manic event, most commonly hypomania. This observation is consistent with the hypothesis that bipolar I disorder may be stabilized from the depressive pole of the illness.[17,18] Although the reduction in overall manic events observed in this study was important clinically, the reported incidence was higher than that in the controlled monotherapy maintenance trials.[17,18] Interestingly, of the patients reporting some form of manic event in the continuation study, one third had used concomitant antidepressants and 1 in 5 had used antidepressants within 1 month of their manic episode; the higher rates of overall manic events found in this study compared with the others may therefore reflect differential adjunctive therapy. Importantly, in this study,

as in the controlled maintenance trials, lamotrigine improved bipolar depression without inducing manic switch or cycle acceleration.

The results of 2 placebo-controlled maintenance studies that compared lamotrigine with placebo and lithium in recently manic and depressed bipolar I patients, respectively, demonstrated that lamotrigine significantly delayed time to a depressive episode, whereas lithium significantly delayed time to a manic episode.[17,18] A meta-analysis of these studies confirmed the original study findings and demonstrated improved mood stability at both poles of the illness for lamotrigine-treated patients,[21] supporting present observations of reduced mood instability during long-term treatment with lamotrigine.

The pattern of concomitant medication use in the present study provided insight into typical psychiatric practice, as well as the potential long-term psychotropic medication needs of bipolar I patients receiving lamotrigine therapy. Only half of the patients required concomitant psychotropic medication during 1 year of lamotrigine treatment, most commonly benzodiazepines for treatment of agitation and anxiety. Few patients received additional mood stabilizers, and those patients who did used these medications inconsistently. Therefore, conclusions regarding differential effects of lamotrigine with or without concomitant mood stabilizers could not be made. Nearly a third of the patients in the study received concomitant antidepressant treatment, which in the absence of a mood stabilizer could have precipitated mania and caused mood instability.[11–13] The potential reduction in manic, hypomanic, and mixed states observed in this study, in light of minimal use of traditional mood stabilizers, may indicate that lamotrigine has mood-stabilizing activity to counteract the risk of manic switch with antidepressant therapy and requires additional study. Importantly, lamotrigine appeared well tolerated when used in combination with a variety of psychotropic medications used to treat bipolar disorder.

This study has several important methodological limitations. The lack of a randomized, double-blind, placebo-controlled design and use of concomitant psychotropic medications preclude attributing the observed antidepressant and possible mood-stabilizing effects entirely to lamotrigine. Rather, additional contributions to response could be attributed to placebo response, investigator or patient bias, concomitant medications, or spontaneous remission. Retrospective patient self-report formed the basis for assessment of mood stability. Although the recall period was limited to the year prior to study participation, patients may have overestimated or underestimated the historical incidence of mania, hypomania, or mixed mood episodes. Despite these limitations, the open-label, flexible-dose study design and use of combination therapy simulated naturalistic clinical practice, albeit in a select patient population from a clinical trial. Further, although the 1-year duration of this study may have contributed to patient attrition, it provided data regarding lamotrigine's effectiveness and tolerability over the long term.

In summary, lamotrigine as monotherapy or adjunctive therapy was effective and well tolerated for depression in bipolar I patients for up to 1 year of treatment. Moreover, compared with a 1-year retrospective assessment, fewer manic, hypomanic, and mixed events were identified prospectively. Although open-label, this study adds to the growing evidence that lamotrigine has acute and long-term antidepressant effectiveness in bipolar I depression. Effectiveness in acute depression has also been demonstrated in patients with treatment-refractory depression[25] and rapid-cycling bipolar II disorder.[26] Importantly, no cases of serious rash were reported. Lamotrigine's profile as adjunctive therapy for bipolar depression needs further investigation.

Drug names: bupropion (Wellbutrin and others), carbamazepine (Carbatrol, Tegretol, and others), chlorpromazine (Thorazine, Sonazine, and others), gabapentin (Neurontin and others), lamotrigine (Lamictal), mirtazapine (Remeron and others), nefazodone (Serzone and others), olanzapine (Zyprexa), perphenazine (Trilafon and others), primidone (Mysoline and others), risperidone (Risperdal), trazodone (Desyrel and others), venlafaxine (Effexor), zolpidem (Ambien).

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