A Pooled Analysis of 2 Placebo-Controlled 18-Month Trials of Lamotrigine and Lithium Maintenance in Bipolar I Disorder

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Background: Two clinical trials, prospectively designed for combined analysis, compared placebo, lithium, and lamotrigine for treatment of bipolar I disorder in recently depressed or manic patients.

Method: 1315 bipolar I patients (DSM-IV) enrolled in the initial open-label phase, and 638 were stabilized and randomly assigned to 18 months of double-blind monotherapy with lamotrigine (N = 280; 50–400 mg/day fixed dose or 100–400 mg/day flexible dose), lithium (N = 167; serum level of 0.8–1.1 mEq/L), or placebo (N = 191). The primary endpoint was time from randomization to intervention for a mood episode. Data were gathered from August 1997 to August 2001.

Results: Lamotrigine and lithium were superior to placebo for time to intervention for any mood episode (median survival: placebo, 86 days [95% CI = 58 to 121]; lithium, 184 days [95% CI = 119 to not calculable]; lamotrigine, 197 days [95% CI = 144 to 388]). Lamotrigine was superior to placebo for time to intervention for depression (median survival: placebo, 270 days [95% CI = 138 to not calculable]; lithium, median not calculable; lamotrigine, median not calculable). Lithium and lamotrigine were superior to placebo for time to intervention for mania (median survival not calculable for any group). Results of additional analyses adjusted for index mood were similar; however, only lithium was superior to placebo for intervention for mania. There was no evidence that either active treatment caused affective switch. Adverse event analysis indicated more diarrhea (19% vs. 7%, $p < .05$) and tremor (15% vs. 4%, $p < .05$) in lithium-treated patients compared with lamotrigine-treated patients.

Conclusions: Lamotrigine and lithium stabilized mood by delaying the time to treatment for a mood episode. Lamotrigine was effective against depression and mania, with more robust activity against depression. Lithium was effective against mania.

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Bipolar disorder is a serious and recurrent psychiatric illness characterized by fluctuating episodes of elevated and depressed mood. Bipolar I disorder affects 1.2% to 1.6% of the population,[1,2] but this prevalence increases to 3.4% when the full spectrum of bipolar disorders is included.[3,4] Bipolar I and II disorders are highly recurrent illnesses with considerable attendant morbidity,[5,6] especially during depressive and mixed phases. Depression constitutes a majority of time spent with affective symptoms, outstripping mania and hypomania by a ratio of 3:1 in bipolar I and 37:1 in bipolar II patients.[4] Patients with bipolar disorder have a lifetime mortality by suicide of up to 20%, much higher than that of the general population, and suicide represents the major cause of death in younger patients with bipolar disorder.[7–10] Bipolar disorder is also associated with significant psychosocial impairment, with deficits measurable as long as 2 years after recovery.[11–13] These functional difficulties are due in part to persistent depressive symptoms that occur between mood episodes.[13] Further, 30% to 60% of individuals diagnosed with bipolar disorder fail to regain full function in terms of vocational and social performance with current treatment strategies.[14] These clinical features of bipolar disorder highlight the pressing need for improved understanding and long-term management, especially during the depressive phase of the illness.

The most recent American Psychiatric Association guidelines for treatment of bipolar disorder distinguish acute therapy targeted against index mood episode and long-term maintenance therapy to prevent further episodes. Initiation of lithium or lamotrigine therapy is the recommended first-line treatment for acute bipolar depression in these guidelines.[15] However, maintenance treatment is the major clinical challenge in this chronic disorder. Lamotrigine is an anticonvulsant approved for the long-term treatment of epilepsy with demonstrated efficacy in 2 randomized, double-blind, placebo-controlled clinical trials of acute treatment in bipolar I depression.[16–18] The long-term use of lamotrigine in bipolar I patients has previously depended on clinical anecdote,[19] open-label experience,[20] and 1 placebo-controlled rapid-cycling study.[21]

Lithium has been considered the cornerstone of maintenance therapy for bipolar disorder for many years. However, until recently, evidence for its use has depended on relatively few well-controlled trials, only a small proportion of which recruited bipolar patients only, limiting confidence in the magnitude of efficacy against manic and depressive relapse individually.[22–24] Lithium also has a significant side effect burden at recommended serum drug levels (0.8–1.0 mEq/L),[25] a narrow therapeutic ratio, and a risk of neurotoxicity and even fatality in overdose. While falling well short of the ideal treatment it has been believed to be, lithium provides an appropriate comparator for new compounds. Furthermore, new data on lithium's efficacy would significantly strengthen the evidence base on which its continued use depends.

We present the results of a pooled analysis of two 18-month, placebo-controlled, double-blind clinical trials, Study M (GW606/2006) and Study D (GW605/2003), that were prospectively designed for combined comparison of lamotrigine and lithium versus placebo for maintenance treatment in bipolar I disorder following recent manic[26] and depressive[27] episodes. This analysis allows a more highly powered assessment of the main treatment effects of lamotrigine and lithium and their relative efficacy on manic and depressive relapse, specifically. A pooled analysis also permits investigation of key subsidiary issues that include the contribution of early relapses to the overall study results, rates of switching of patients from depression into mania and vice versa, the effects of illness severity and cycle frequency, and past history of lithium use. These findings will inform current practice and provide the basis for new studies to improve treatment strategies for bipolar disorder.

METHOD

Two 18-month, placebo-controlled, double-blind clinical trials were prospectively designed for combined analysis of lamotrigine and lithium versus placebo as maintenance treatment in bipolar I disorder following index manic and depressive episodes. Each study enrolled adult (≥ 18 years of age) outpatients who were currently or recently manic or hypomanic or had experienced mixed mood states (Study M; GW606/2006) or who were currently or recently depressed (Study D; GW605/2003) according to DSM-IV criteria within 60 days of screening. Data were gathered from August 1997 to August 2001. Separate reports of both clinical trials have been published elsewhere.[26,27] Patients with more than 6 mood episodes in the past year; panic disorder, obsessive-compulsive disorder, social phobia, or bulimia nervosa in the year prior to study participation; or recent substance abuse and patients who were actively suicidal, had a score of ≥ 3 on item 3 (suicidal thoughts) of the Hamilton Rating Scale for Depression (HAM-D), or had significant thyroid abnormality were excluded.[26,27]

Screening and Open-Label Phases

Eighty-three investigators from 18 countries participated in the 2 clinical trials. Institutional review boards at each site approved the protocols, and all patients provided written informed consent prior to study enrollment.

Patients were evaluated for study enrollment during a 2-week screening phase. Those meeting enrollment criteria completed an 8- to 16-week open-label phase during which all patients received lamotrigine (target dose = 200 mg/day, minimum dose = 100 mg/day) as adjunctive therapy or monotherapy while other psychotropic drugs were progressively discontinued. Lamotrigine was initiated at a dose of 25 mg/day for the first 2 weeks of therapy (12.5 or 50 mg/day when combined with valproate or carbamazepine, respectively), 50 mg/day for the next 2 weeks (25 or 100 mg/day when combined as above), and 100 mg/day for the next 2 weeks (50 or 200 mg/day when combined as above) and thereafter was increased in 100-mg/day increments every 2 weeks as needed (50-mg increments when combined with valproate). Lithium treatment was discontinued over a minimum period of 3 weeks. Patients who reached a stable dose of lamotrigine monotherapy by week 8 of the open-label phase and met response criteria (defined as a Clinical Global Impressions-Severity of Illness scale [CGI-S] score ≤ 3 maintained for at least 4 continuous weeks) were eligible to enroll in the double-blind phase. Patients who did not meet response criteria at the end of 16 weeks of open-label treatment with lamotrigine were to be discontinued from the study.

Double-Blind Phases

In Study D, patients were randomly assigned equally to one of 5 treatment groups: lamotrigine (50, 200, or 400 mg/day), lithium (titrated to serum levels of 0.8–1.1 mEq/L), or placebo for up to 18 months. In Study M, patients were randomly assigned equally to lamotrigine

(flexible dose of 100–400 mg/day based on clinical response; starting dose of 200 mg/day), lithium (titrated to serum drug levels of 0.8–1.1 mEq/L), or placebo. Study D was later amended to reduce the number of lamotrigine treatment groups at randomization from 3 to 1 (200 mg/day), and an a priori decision was made to combine the 200- and 400-mg/day lamotrigine groups for the primary efficacy analysis. Elimination of the 50-mg/day dose was based on the hypothesis that this dose would be subtherapeutic.[16] In Study M, the lithium treatment arm was closed halfway through enrollment to divert new patients into the lamotrigine and placebo groups. Study M was terminated prior to full enrollment. No interim analyses or other types of unblinding were used to reach any of these administrative decisions.

Double-blind, double-dummy packs of 25- and 100-mg dispersible lamotrigine tablets, 300-mg lithium carbonate tablets, and matching placebo were used in both studies such that patients took either active lamotrigine and placebo lithium, placebo lamotrigine and active lithium, or placebo lamotrigine and placebo lithium. Clinic visits were scheduled weekly during the open-label phase and the first 4 weeks of the double-blind phase, every 2 weeks through week 8 of the double-blind phase, and then every 4 weeks through week 76. At each clinic visit, laboratory tests were performed 8 to 12 hours after the last dose of study medication. When a lithium dose adjustment was indicated, matching laboratory reports detailing the adjustment were issued for that patient and 2 subsequent placebo lithium patients selected by the laboratory to maintain the blind.

Adverse events, defined as any untoward medical event regardless of attribution, were queried at each clinic visit. At the week 52 clinic visit, patients who had not experienced a relapse or recurrence of a mood episode were allowed to continue with double-blind treatment through week 76; those who had been treated for a relapse or recurrence were discontinued from the study.

Measures

The primary efficacy endpoint was the time to intervention (defined as addition of pharmacotherapy or electroconvulsive therapy) for any mood episode (relapse or recurrence of a manic, hypomanic, mixed, or depressive episode). Secondary measures included time to intervention for depression and time to intervention for mania. Patients who discontinued from the study for reasons other than the defined events for the primary analysis were censored at the time of dropout. To confirm that the censoring of these events did not distort the pattern of results, another censoring method was employed in which all dropouts were included as events in the survival analysis (survival in study). Tolerability was examined using adverse events and changes from baseline in laboratory test results and vital signs.

Statistical Analyses

Data from both studies were combined following between-study comparison of baseline and demographic variables by Fisher exact test (gender) or analysis of variance (all others); significant differences were determined using a 2-tailed comparison alpha level of .05. The efficacy population comprised all patients randomly assigned to treatment during the double-blind phases who received at least 1 dose of study medication and provided at least 1 postbaseline efficacy outcome assessment. The safety population comprised all patients who took at least 1 dose of study medication. Kaplan-Meier survival curves were generated for time-to-event data. Differences among treatment groups were assessed using log-rank tests at an $\alpha = .05$ level of significance using combined data. Additional analyses of time to intervention for mood episode and depressive and manic events were adjusted for study (index mood). All time-to-event analyses were tested for study-by-treatment interactions, none of which were statistically significant. Hazard ratios for intervention for depression and mania were calculated using Cox proportional hazard models, and differences among treatment groups were assessed using Wald statistics. Hazard ratios were not corrected for index mood. Differences in proportions of subjects completing the study were compared using Mantel-Haenszel chi-square tests adjusted for investigator.

The incidence of adverse events in the safety population was summarized by phase of the study. Laboratory and vital signs data were analyzed for frequency of clinically significant shifts. Frequency data were analyzed using the Fisher exact test.

RESULTS

Sample

To test the comparability of the 2 study populations, a number of demographic and baseline illness characteristics were compared between each study. Significant differences between studies (Study M vs. Study D) were noted for the following parameters without correction for multiple comparisons: mean age at screening (41.1 vs. 43.4 years), duration of illness (18.5 vs. 21.3 years), number of depressive episodes in the past 1 and 3 years (1.0 vs. 1.7 and 2.4 vs. 3.8, respectively), number of manic episodes in the past 1 and 3 years (1.4 vs. 0.8 and 3.0 vs. 2.2, respectively), number of mixed episodes in the past 3 years (0.6 vs. 0.4), and Global Assessment Scale score at screening (48 vs. 51). There were no significant differences for the following parameters: gender, age at onset of first depressive episode, age at onset of first manic episode, number of hypomanic episodes in the past 1 and 3 years, number of mixed episodes in the past year, total number of mood episodes in the past 1 and 3 years, and CGI-S score at screening. Although the majority of the

Table 1. Patient Demographics and Characteristics for the Combined Study Populations From 2 Studies of Bipolar I Patients[a]

Characteristic	Open-Label Phase Total (N = 1305)	Double-Blind Phase Placebo (N = 190)	Double-Blind Phase Lithium (N = 166)	Double-Blind Phase Lamotrigine (N = 227)
Age, mean, y	42	42	43	43
Female, N (%)	763 (58)	95 (50)	96 (58)	131 (58)
No. of mood episodes in past year, mean				
Depression	1.5	1.5	1.5	1.4
Mania	1.0	1.2	1.0	0.9
Hypomania	0.3	0.3	0.3	0.3
Mixed states	0.1	0.2	0.2	0.1
CGI-S score, mean	4.4	4.4	4.2	4.3
GAS score, mean	49.4	50.0	50.8	50.2
Psychiatric history, N (%)				
Relative with bipolar disorder	362 (28)	48 (25)	48 (29)	50 (22)
Relative with major depressive episode	452 (35)	57 (30)	54 (33)	79 (35)
Psychotic episodes	460 (35)	64 (34)	56 (34)	71 (31)
Suicide attempts	455 (35)	56 (29)	61 (37)	75 (33)
Psychiatric hospitalizations	858 (66)	120 (63)	107 (64)	131 (58)
Psychotropic medication use	1235 (95)	177 (93)	157 (95)	211 (93)

[a]Data shown are for the safety population (200-mg + 400-mg + flexible-dose lamotrigine treatment groups).
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, GAS = Global Assessment Scale.

Table 2. Patient Accountability for 2 Pooled Studies of Bipolar I Patients[a]

Characteristic	Open-Label Phase (N = 1315)	Double-Blind Phase Total (N = 638)	Double-Blind Phase Placebo (N = 191)	Double-Blind Phase Lithium (N = 167)	Double-Blind Phase Lamotrigine (N = 280)
Completed study phase	664 (50)	74 (12)	12 (6)	21 (13)	41 (15)[b]
Received intervention for a mood episode		332 (52)	115 (60)	74 (44)[b]	143 (51)
Mania		123 (19)	47 (25)	18 (11)[b]	58 (21)[c]
Depression		209 (33)	68 (35)	56 (33)	85 (30)
Discontinued prematurely	651 (50)	232 (36)	64 (34)	72 (43)	96 (34)
Did not meet randomization criteria	79 (6)	NA	NA	NA	NA
Adverse event	169 (13)	68 (11)	15 (8)	30 (18)[d]	23 (8)[e]
Consent withdrawn	154 (12)	54 (8)	16 (8)	15 (9)	23 (8)
Lost to follow-up	90 (7)	30 (5)	8 (4)	8 (5)	14 (5)
Protocol violation	29 (2)	14 (2)	3 (2)	4 (2)	7 (3)
Other (missing data)	130 (10)	67 (11)	23 (12)	15 (9)	29 (10)

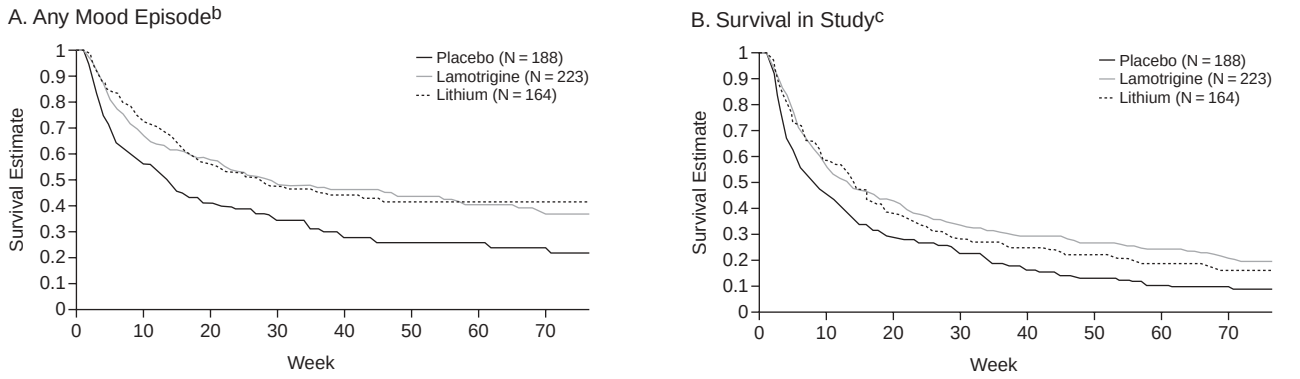
[a]Values shown as N (%). Data shown are for all patients, including the 50-mg lamotrigine treatment group.
[b]$p < .05$ for active treatment vs. placebo, Mantel-Haenszel chi-square test (adjusted for investigator).
[c]$p < .05$ for lithium vs. lamotrigine, Mantel-Haenszel chi-square test (adjusted for investigator).
[d]$p < .01$ for active treatment vs. placebo, Fisher exact test.
[e]$p < .01$ for lithium vs. lamotrigine, Fisher exact test.
Abbreviation: NA = not applicable.

between-study differences were not judged to be of clinical or prognostic significance, differences were observed in relative frequency of prior manic versus depressive episodes. Time-to-event data were analyzed both adjusted and unadjusted for index episode (i.e., study). Unless otherwise noted, results were similar for both methods, in which case unadjusted analyses are presented.

Patient characteristics for the combined sample (excluding the 50-mg lamotrigine treatment group) are presented by study phase and treatment group in Table 1. Nearly all patients had previously received medication for a mood-related episode, and approximately two thirds of patients had required psychiatric hospitalization in their lifetimes. One third of all patients had a history of attempted suicide. Depending on treatment group, 56% to 60% of patients had received prior lithium treatment at some point, with 17% to 18% of these patients having failed to achieve good clinical response and 10% to 12% not having tolerated such prior treatment (data not shown). Overall demographic and disease characteristics of the combined sample were comparable across treatment groups and indicative of moderate severity of illness.

Patient accountability for the combined sample is presented in Table 2. Study D enrolled 966 patients and Study M enrolled 349 patients (N = 1315) into initial open-label treatment. Ten patients who enrolled did not continue or had incomplete data and were not included in the analysis. Approximately half of the patients completed open-label stabilization and were randomly assigned to double-blind treatment (N = 638: N = 191 placebo, N = 167 lithium, and N = 280 lamotrigine). The 83 enrolling study sites each randomized a median of 5 patients (range, 1–35 pa-

Figure 1. Time to (A) Intervention for a Mood Episode and (B) Discontinuation From Study for the Efficacy Population: Kaplan-Meier Curves[a]



[a]Mean lamotrigine dosage was 245 mg/day and mean serum lithium level was 0.7 mEq/L. Median (95% CI) times to intervention for a mood episode were 86 (58 to 121), 184 (119 to not calculable), and 197 (144 to 388) days for the placebo, lithium, and lamotrigine groups, respectively.
[b]Lamotrigine vs. placebo, $p < .001$; lithium vs. placebo, $p < .001$; lamotrigine vs. lithium, $p = .629$.
[c]Lamotrigine vs. placebo, $p < .001$; lithium vs. placebo, $p = .006$; lamotrigine vs. lithium, $p = .491$.

Table 3. Comparison of Overall Efficacy and Early Relapse Using Survival Data[a]

	All Events		Events in First 28 Days Excluded	
Efficacy Measure	No. of Events, N (%)	Median Survival, d (95% CI)	No. of Events, N (%)	Median Survival, d (95% CI)
Time to intervention for a mood episode[b]				
Placebo	115 (61)	86 (58 to 121)	75 (52)	162 (99 to 237)
Lithium	74 (45)	184 (119 to NC)[c]	59 (40)	243 (146 to NC)[c]
Lamotrigine	111 (50)	197 (144 to 388)[c]	82 (43)	374 (197 to NC)[c]
Survival in study[d]				
Placebo	165 (88)	52 (34 to 75)	120 (84)	86 (69 to 111)
Lithium	133 (81)	89 (72 to 114)[c]	115 (79)	104 (86 to 139)
Lamotrigine	174 (78)	86 (62 to 128)[c]	143 (74)	130 (86 to 164)[c]

[a]Data shown are for the efficacy population: placebo N = 188, lithium N = 164, lamotrigine N = 223.
[b]Primary endpoint = the time to intervention (defined as addition of pharmacotherapy or electroconvulsive therapy) for any mood episode (relapse or recurrence of a manic, hypomanic, mixed, or depressive episode). Patients who discontinued from the study for reasons other than events for the primary analysis were censored at the time of dropout. An additional censoring method was employed.
[c]$p < .05$ vs. placebo; differences in survival distributions between active treatment and placebo were tested using a log-rank test.
[d]Survival in study, in which all dropouts were included as events in the analysis.
Abbreviation: NC = not calculable.

tients). Proportionately more patients treated with lithium (18%) discontinued prematurely from double-blind treatment due to an adverse event compared with placebo (8%) and lamotrigine (8%).

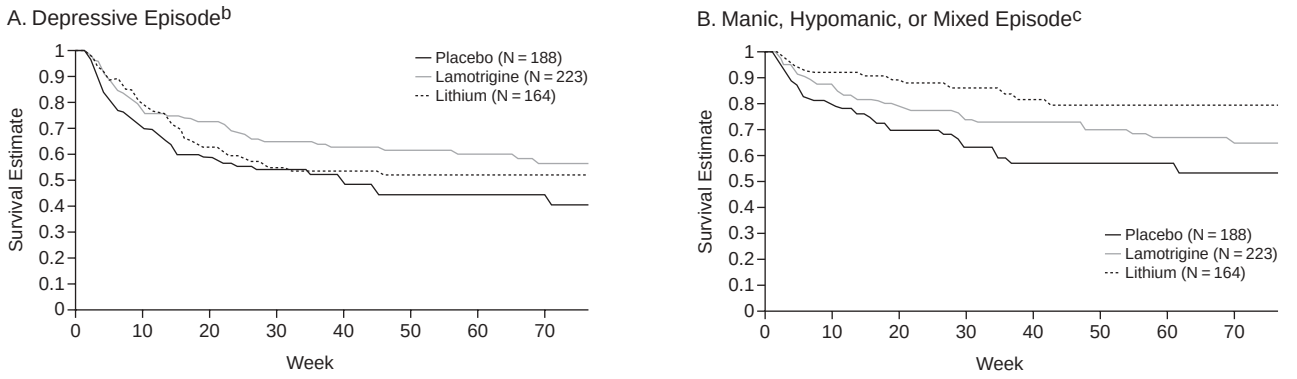
Efficacy

Time to intervention. Both lamotrigine and lithium were superior to placebo for time to intervention for a mood episode (lamotrigine vs. placebo, $p < .001$; lithium vs. placebo, $p < .001$; Figure 1A). Lamotrigine and lithium were not statistically different ($p = .629$). Median times to intervention (with 95% CIs) were 86 (58 to 121), 184 (119 to not calculable [NC]), and 197 (144 to 388) days for the placebo, lithium, and lamotrigine groups, respectively (Table 3). Similar results were obtained when all early dropouts were included as events in the analysis (Figure 1B; survival in study: median times to intervention [95% CI] were 52 [34 to 75], 89 [72 to 114], and 86 [62 to 128] days for the placebo, lithium, and lamotrigine groups; lamotrigine vs. placebo, $p < .001$; lithium vs. placebo, $p = .006$; lamotrigine vs. lithium, $p = .491$).

In the placebo group, 6% (12/188) of the patients completed 18 months of monotherapy without treatment intervention compared with 13% (21/164) in the lithium group (lithium vs. placebo, $p = .101$) and 14% (32/223) in the lamotrigine groups (lamotrigine vs. placebo, $p = .012$).

Lamotrigine, but not lithium, was statistically superior to placebo at prolonging the time to intervention for a depressive episode (median survival [95% CI]: placebo, 270 days [138 to NC]; lithium, NC; lamotrigine, NC; lamotrigine vs. placebo, $p = .009$; lithium vs. placebo, $p = .120$; Figure 2A); lamotrigine and lithium were not statistically different ($p = .325$). For patients receiving treatment intervention for depression, mean (SD) HAM-D scores at the time of intervention were placebo, 18.6 (6.1); lithium, 18.8 (7.1); and lamotrigine, 18.6 (7.0). The percentages of

Figure 2. Time to Intervention for (A) Depressive Episode and (B) Manic, Hypomanic, or Mixed Episode for the Efficacy Population: Kaplan-Meier Curves[a]



[a]Mean lamotrigine dosage was 245 mg/day and mean serum lithium level was 0.7 mEq/L. Median time to intervention for depression (95% CI) was 270 days (138 to not calculable) for placebo; these values were not calculable for the lithium or lamotrigine group.
[b]Lamotrigine vs. placebo, p = .009; lithium vs. placebo, p = .120; lamotrigine vs. lithium, p = .325.
[c]Lamotrigine vs. placebo, p = .034; lithium vs. placebo, p < .001; lamotrigine vs. lithium, p = .030.

patients meeting DSM-IV criteria for a depressive episode up to and including the time of treatment intervention were placebo, 33%; lithium, 31%; and lamotrigine, 26%.

Lithium and lamotrigine were statistically superior to placebo at prolonging the time to intervention for a manic, hypomanic, or mixed episode (median survival not calculable for any group: lithium vs. placebo, p < .001; lamotrigine vs. placebo, p = .034; Figure 2B); lithium was superior to lamotrigine (p = .030). For patients receiving treatment intervention for mania, mean (SD) scores on the 11-item Mania Rating Scale (from the Schedule for Affective Disorders and Schizophrenia–change version[28]) at the time of intervention were placebo, 14.0 (10.0); lithium, 14.0 (9.9); lamotrigine, 15.7 (10.2). The percentages of patients meeting DSM-IV criteria for a manic, hypomanic, or mixed episode at the time of intervention were placebo, 25%; lithium, 12%; and lamotrigine, 22% (lithium vs. placebo, p = .002; lamotrigine vs. lithium, p = .011; lamotrigine vs. placebo, p = .487).

Additional analyses, adjusted for index mood, yielded essentially the same results as the aforementioned analyses for time to intervention for any mood episode and time to intervention for a depressive episode. However, when mood was adjusted for, only lithium remained significant for time to intervention for mania (lithium vs. placebo, p < .001; lamotrigine vs. placebo, p = .149; lithium vs. lamotrigine, p = .024).

Risk of intervention for depression or mania. The relative risk for intervention over time was assessed using hazard ratios (HRs). Compared with placebo, relative risk for intervention for depression was significantly reduced by lamotrigine (HR = 0.637, 95% CI = 0.453 to 0.895, p = .009), representing a 36% reduction in the risk of depressive relapse. A nonsignificant reduction in risk for depressive relapse was observed for the lithium group (HR = 0.760, 95% CI = 0.533 to 1.082, p = .128, 24% reduction). The risk for intervention for depression was lower for lamotrigine compared with lithium but was not significant (HR = 0.838, 95% CI = 0.586 to 1.198, p = .333, 16% reduction).

The relative risk of intervention for mania was significantly reduced for both lithium and lamotrigine compared with placebo (lithium: HR = 0.353, 95% CI = 0.205 to 0.608, p < .001, 64% reduction; lamotrigine: HR = 0.642, 95% CI = 0.427 to 0.966, p = .033, 36% reduction). Lithium-treated patients had a lower risk of intervention for mania compared with lamotrigine-treated patients (HR = 0.550, 95% CI = 0.319 to 0.949, p = .032, 45% reduction).

Polarity of relapse events. Depression (N = 189) outnumbered the episodes of elevated mood (mania, hypomania, or mixed states, N = 111) in patients who required intervention for an emerging mood episode during the randomized phase. When the index episode was mania, 2 of the 3 treatment groups had a higher ratio of relapse of mania compared with depression (placebo = 1.4, lithium = 0.8, lamotrigine = 2.4). When the index episode was depression, all 3 treatment groups had a higher ratio of relapse of depression compared with mania (placebo = 2.4, lithium = 4.8, lamotrigine = 2.1). There was no evidence that, compared with placebo, either lithium or lamotrigine caused switching to the opposite pole of the illness as assessed by either frequency of intervention or meeting DSM-IV criteria for mania, hypomania, depression, or mixed states.

Effects of early relapse. Early relapse may occur as a result of acute withdrawal of active treatment, specifically, lithium. Such effects may distort the findings of relapse prevention studies. To examine the effect of early relapse, time to intervention for a mood episode and survival in study were analyzed excluding patients who relapsed to

Table 4. Time to Intervention for a Mood Episode Among Study Subpopulations From 2 Pooled Studies of Bipolar I Patients

Population	Median Time to Intervention, d (95% CI)		
	Placebo	Lithium	Lamotrigine
All patients (N = 638)	86 (58 to 121)	184 (119 to NC)	197 (144 to 388)
Subpopulations			
Recent lithium treatment[a] (N = 146)	30 (18 to 58)	184 (114 to NC)[b]	197 (58 to 453)[b]
No recent lithium treatment (N = 429)	111 (85 to 183)	187 (101 to 310)	202 (130 to 482)[b]
CGI score of 3 at randomization (N = 138)	75 (44 to 203)	184 (49 to NC)	310 (146 to NC)[b]
CGI score < 3 at randomization (N = 437)	87 (58 to 138)	197 (119 to NC)[b]	163 (114 to 374)[b]
< 4 Episodes in past year (N = 406)	86 (58 to 162)	212 (139 to NC)[b]	256 (146 to 472)[b]
4–6 Episodes in past year (N = 169)	87 (34 to 146)	123 (80 to NC)	146 (86 to 197)

[a]Defined as a course of lithium treatment within the past 5 months leading to serum levels ≥ 0.4 mEq/L for at least 1 month.
[b]p < .05 vs. placebo; differences in survival distributions between treatments were tested using a log-rank test.
Abbreviation: NC = not calculable.

the index episode during the first 28 days of the double-blind phases (Table 3). Lamotrigine significantly prolonged time to intervention for a mood episode and survival in study, regardless of the effects of early relapse. Lithium did not prolong survival in study when early-relapse patients were excluded from analysis.

Treatment response in subpopulations. Exploratory analyses were carried out on study subpopulations that were prospectively defined. Approximately one fifth of patients had been stabilized on lamotrigine monotherapy during the initial open-label study phases. In the subsequent double-blind phases, time to intervention for a mood episode did not differ significantly between treatment groups in this subpopulation, although median survival estimates were numerically greater than placebo for both lithium and lamotrigine, with the latter trending toward significance (p = .058). Survival estimates for patients initially stabilized on polytherapy were similar to the overall results—both lamotrigine and lithium significantly prolonged time to intervention compared with placebo (data not shown).

Approximately one fifth of the study population had received lithium treatment within the prior 5 months at doses sufficient to attain minimum serum levels of 0.4 mEq/L for at least 1 month. In this subpopulation, time to intervention was significantly prolonged by both lithium and lamotrigine monotherapy compared with placebo (Table 4). This subgroup showed a relatively short (4-week) median time to intervention in the placebo group, suggesting some contribution from discontinuation of previous lithium treatment. Among patients who had not recently taken lithium prior to study entry, time to intervention for a mood episode, compared with placebo, was significantly greater for lamotrigine (p = .029) but not lithium (p = .093).

Patients could enter the double-blind study phases with a CGI-S score of 3 (mildly ill) or less. Among the approximately one fifth of the study population with a CGI score of 3 at randomization (minimal stability criterion), time to intervention was significantly greater with lamotrigine compared with placebo, with a trend for lithium versus placebo (Table 4). Survival estimates for patients randomized with a CGI score < 3 appeared similar to the overall results.

Patients were eligible to enter the screening phase if they had experienced no more than 6 mood episodes during the prior year. Within the subpopulation of patients meeting DSM-IV episode frequency criteria for rapid cycling (in this case, 4–6 episodes during the past year), time to intervention did not differ significantly among treatment groups, although survival estimates were numerically greater than placebo for both lithium and lamotrigine, with the former trending toward significance (p = .077, Table 4). Survival estimates for patients who had experienced fewer than 4 episodes during the past year appeared to be similar to the overall results.

Tolerability

Among all patients treated in the open-label phase, the most common treatment-emergent adverse events were headache (25%), nausea (12%), infection (11%), rash (11%), and dizziness (10%). The most common adverse events during the double-blind phase were headache (19% placebo and lamotrigine, 15% lithium), nausea (11% placebo, 14% lamotrigine, 20% lithium), and diarrhea (8% placebo, 7% lamotrigine, 19% lithium). Overall, the incidence of adverse events reported in the lamotrigine group across both phases of the study was similar to that in the placebo group. Significantly more lithium-treated patients reported nausea, diarrhea, somnolence, and tremor compared with those treated with placebo (Table 5). More diarrhea and tremor were reported by patients treated with lithium compared with lamotrigine (p < .05).

Significantly more patients treated with lithium experienced an adverse event leading to discontinuation from the study compared with those taking lamotrigine or placebo, respectively (tremor: 5% vs. < 1% and 1%; p < .05; nausea: 8% vs. < 1% and 1%; p < .05; somnolence: 4% vs.< 1% and < 1%; p < .05).

The incidence of nonserious rash was similar across treatment groups. There was 1 case of mild Stevens-

Table 5. Adverse Events Occurring in ≥ 10% of Patients in 2 Pooled Studies of Bipolar I Patients (%)

Adverse Event	Open-Label Phase (N = 1305)	Randomized Phase		
		Placebo (N = 190)	Lithium (N = 166)	Lamotrigine (N = 227)
Headache	25	19	15	19
Nausea	12	11	20[a]	14
Infection	11	13	13	13
Rash	11	5	5	7
Dizziness	10	9	8	7
Somnolence	9	7	13[a]	9
Diarrhea	8	8	19[a,b]	7
Insomnia	8	6	10	10
Tremor	4	5	15[a,b]	4

[a]p < .05 lithium vs. placebo.
[b]p < .05 lithium vs. lamotrigine.

Johnson syndrome reported 31 days after initiation of lamotrigine in the open-label phase of Study D that was classified as nonserious rash, since hospitalization was not required. A case of rash involving hospitalization was reported in the open-label phase of Study M and described as moderately severe maculopapular nonpruritic facial rash associated with facial erythema that resolved following discontinuation of the drug without further treatment.

Three patients committed suicide during Study D, 2 in the preliminary phase and 1 in the double-blind phase (lamotrigine group). No patients attempted suicide in either phase of Study M.

The proportions of patients with clinically important elevations in laboratory values from randomization through the last recorded value of the double-blind phase were creatinine: placebo < 1%, lithium 5%, lamotrigine 1% and alanine aminotransferase (ALT): placebo 4%, lithium 6%, lamotrigine 3%. Thyroid-stimulating hormone (placebo < 1%, lithium 8%, lamotrigine 0%) was elevated from screening.

DISCUSSION

This pooled analysis from 2 large placebo-controlled studies of lithium and lamotrigine as maintenance treatment for bipolar I disorder presents a highly powered assessment of the efficacy and tolerability of these pharmacologic agents at both extremes of the illness. In addition to lamotrigine's well-described effect of delaying intervention for depression, the present analysis sheds new light on the efficacy of lamotrigine in delaying intervention for mania, as well as the impact of early relapse, illness severity, and prior treatment patterns on overall efficacy. The findings may provide the basis for new strategies to improve treatment outcomes in bipolar I disorder.

Lamotrigine monotherapy significantly delayed the time to depression compared with placebo, again confirming findings of the individual studies[26,27] and those conducted in acute bipolar depression,[16] bipolar II patients with rapid cycling,[21] and patients refractory to treatment or intolerant of lithium.[17] The results for patients maintained after an episode of mania were the same as for those treated on a long-term basis after an episode of depression. No maintenance study in a recently depressed bipolar I sample has previously existed for such a comparison. The combined analysis also detected a delay in time to intervention for mania with lamotrigine compared with placebo, although lithium showed a more robust effect on this measure. Based on the results of this pooled analysis, lamotrigine has demonstrated a therapeutic benefit against mania as well as depression, although efficacy was most robust against depression. There was no suggestion that lamotrigine increased the rate of switch to the opposite pole of the illness. These data confirm the increasing evidence of lamotrigine's efficacy in bipolar disorder and serve to distinguish it from currently available mood stabilizers.

This is one of the largest samples of lithium-treated bipolar I patients reported on and analyzed using survival analytic methods, and it nearly doubles the sample size of bipolar patients randomly assigned to lithium or placebo in previous studies, as many of the earlier studies included unipolar patients.[22] Our sample appears representative of patients predominantly in the middle course of highly recurrent illness, recognizably sharing the demographic features of many outpatients with bipolar disorder. Results from the current pooled analysis provide strong statistical evidence of the efficacy of lithium as maintenance therapy in bipolar I disorder. Lithium was superior to placebo at delaying time to a manic episode, confirming the lithium relapse/recurrence data published nearly 30 years ago by Prien and colleagues[29,30] that demonstrated a significant reduction in the frequency of mood episodes, primarily manic, over a 2-year period. While greatly influencing the use of lithium treatment in bipolar disorder, these early studies were criticized because the discontinuation design may have inflated lithium response rates. This criticism does not apply to the current pooled analysis, as nearly two thirds of the patients studied had not recently received lithium treatment and those patients who had received lithium were slowly weaned from the drug.

The use of survival analysis and large sample sizes in this study allowed greater power and sensitivity to detect specific treatment responses. Yet, lithium did not significantly delay time to a depressive event, a result that contrasts with earlier findings of lithium's efficacy in bipolar depression.[29,30] The studies by Prien and colleagues, conducted in a severely depressed inpatient population, detected an antidepressive effect of lithium despite their small sample size (lithum N = 18, placebo N = 13). The severe nature of the disorder may have contributed to this separation from placebo. In a more representative bipolar I outpatient population, we found that the effect was

weaker, but the lithium sample size for efficacy analysis (N = 166) was also smaller compared with the lamotrigine sample (N = 227). Further, the early lithium studies did not encourage investigators to discontinue patients as soon as patients demonstrated clinical symptoms of relapse. Therefore, direct comparison of data with the current pooled analysis should be made with caution. A recent study also suggested evidence of manic prophylaxis for lithium-treated patients compared with placebo-treated patients, with little evidence of lithium prophylaxis for depression.[31] Overall, the results from the present analysis suggest a small benefit from lithium in bipolar depression.

Early relapse after randomization characterized the present studies and other bipolar disorder maintenance studies.[29,30] After these cases were excluded, treatment response did not change, demonstrating that lithium and lamotrigine were superior to placebo for treatment of recurrence of new mood events. Importantly, when early relapsing patients were excluded, median time to survival for a mood episode increased in all treatment groups, nearly doubling in the lamotrigine group, reaffirming the long-term efficacy of lithium and lamotrigine. While discontinuation of lithium or even a reduction in dose may precipitate manic relapse,[31] the majority of patients in the present studies were not treated in the open-label phase with lithium. Among those who were, there was a tendency toward early relapse at randomization to placebo. Thus, the current studies avoided the bias inherent in selecting a sample enriched for lithium responders, but the sample remained large enough to demonstrate the predicted effect in those lithium-treated patients randomly assigned to placebo. Lamotrigine appeared to protect this patient group from relapse as effectively as lithium did.

The index mood episode was positively predictive of the polarity of the next episode in these studies. Among patients randomly assigned to placebo, a possible illustration of the natural course of bipolar illness, an index episode of mania was followed by an intervention for a manic episode in 70% of patients; an index episode of depression was followed by intervention for depression in an even higher 85% of patients. Overall, of the 332 patients requiring intervention for a mood episode of either polarity, 69% received intervention for an episode of the same polarity as the index episode. Although these findings could be reflective of incomplete recovery from the initial index episode, they are consistent with previous studies,[29,30,32] suggesting that the most immediate risk for bipolar patients is for return of symptoms that are the same polarity as the index episode. This finding has clinical implications in terms of both vigilance for early symptoms of the same pole as the index episode and selection of long-term drug treatments.

Analyses that examined the impact of illness severity at the index episode suggested a lack of differential efficacy for the agents on the basis of initial symptom intensity. The study design did not allow a full test of maintenance phase efficacy among rapid-cycling versus non–rapid-cycling patients. However, the results suggest that neither lamotrigine nor lithium was as effective among patients with 4 to 6 mood episodes in the prior year compared with patients with fewer than 4 episodes in the prior year.

In the preliminary and randomized phases of the study, lamotrigine was well tolerated, with an adverse event profile similar to that of placebo in those phases. Rates of rash with lamotrigine were low, although slightly higher in the preliminary phase. Not unexpectedly, lithium treatment was associated with significantly more diarrhea and tremor than lamotrigine. Further, lithium-treated patients had increases in creatinine, ALT, and thyroid-stimulating hormone values across time, patterns that may require long-term monitoring of kidney, liver, and thyroid function. The present study employed lithium doses that produced currently favored serum drug levels of 0.8 mEq/L. This dosing strategy may influence the interpretation of the results, as some authorities favor lower serum drug levels. Considered together, the efficacy and tolerability profiles of lamotrigine for long-term treatment of bipolar I depression appear superior to those of lithium employed at serum drug levels of 0.8 mEq/L. While tolerability was similar in the preliminary and double-blind phases, patients who were intolerant of lamotrigine could have discontinued during the preliminary phase.

Consistent with the methodology employed in many of the earliest lithium studies and nearly all contemporary bipolar maintenance studies, the current study employed an enriched double-blind discontinuation design in which patients who tolerated the experimental medicine under study (lamotrigine in this case) were eligible for randomization. This design continues to be used in the majority of maintenance studies in psychiatry because it decreases variance in the randomized population of patients and limits exposure to placebo. A number of lines of evidence suggest that in this case, enrichment was unlikely to have introduced systematic bias: (1) a relatively small percentage of patients were eliminated from the preliminary phase due to lack of response (6%) or intolerance (13%) to lamotrigine; (2) less than 10% of the study population reported a previous failure to respond to or tolerate lithium; (3) baseline illness severity, as assessed by psychiatric rating scale scores at study entry, did not differ significantly between those patients who were eventually randomized and those who were not; (4) randomization criteria required only minimal improvement during the preliminary phase; and (5) patients were stabilized on treatment with a diverse variety of other medications in addition to lamotrigine. The latter point is important because it means that, more than in most clinical trials, open-label treatment was comparable with everyday practice.

The large sample size of this combined database provided significant advantages over the individual studies, including increased statistical power to detect treatment differences, especially among subsets of patients. On the basis of the combined analysis of 2 large maintenance studies that enrolled patients at both poles of the illness, lithium and lamotrigine were effective maintenance treatments compared with placebo for bipolar I disorder. Lithium significantly delayed time to a manic episode, but not a depressive episode. Lamotrigine was significant for both mania and depression, with a more robust effect in depression. Thus, lithium and lamotrigine each stabilized mood, but in differing and potentially complementary ways. A key property of a mood stabilizer may not be efficacy against the opposite pole, but neutrality. For a mood stabilizer to be useful as a long-term bipolar treatment, efficacy against one pole of the illness must not make relapse to the opposite pole of the illness more likely. Both lithium and lamotrigine satisfy these criteria and provide potential comparators for future studies.

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

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REFERENCES

1. Regier D, Narrow W, Rae D. The de facto mental and addictive disorders service system: epidemiologic catchment area prospective 1-year prevalence rates of disorders and services. Arch Gen Psychiatry 1993;50:85–94
2. Kessler R, McGonagle K, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. Arch Gen Psychiatry 1994;51:08–19
3. Hirschfeld RMA, Calabrese JR, Weissman MM, et al. Screening for bipolar disorder in the community. J Clin Psychiatry 2003;64:53–59
4. Judd L, Akiskal H, Schettler P, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry 2002;59:530–537
5. Kupka R, Nolen W, Altshuler L, et al. The Stanley Foundation Bipolar Network, 2: preliminary summary of demographics, course of illness and response to novel treatments. Br J Psychiatry 2001;178:S177–S183
6. Kupfer DJ, Frank E, Grochocinski VJ, et al. Demographic and clinical characteristics of individuals in a bipolar disorder case registry [CME]. J Clin Psychiatry 2002;63:120–125
7. Osby U, Brandt L, Correia N, et al. Excess mortality in bipolar and unipolar disorder in Sweden. Arch Gen Psychiatry 2001;58:844–850
8. Dilsaver S, Chen Y-H, Swann A, et al. Suicidality in patients with pure and depressive mania. Am J Psychiatry 1994;151:1312–1315
9. Simpson SG, Jamison KR. The risk of suicide in patients with bipolar disorders. J Clin Psychiatry 1999;60(suppl 2):53–56
10. Schou M. The effect of prophylactic lithium treatment on mortality and suicidal behavior: a review for clinicians. J Affect Disord 1998;50: 253–259
11. Bauwens F, Tracy A, Pardoen D, et al. Social adjustment of remitted bipolar and unipolar out-patients. Br J Psychiatry 1991;159:239–244
12. Coryell W, Scheftner W, Keller M, et al. The enduring psychosocial consequences of mania and depression. Am J Psychiatry 1993;150:720–727
13. Serretti A, Cavallini M, Macciardi F, et al. Social adjustment and self-esteem in remitted patients with mood disorders. Eur Psychiatry 1999; 14:137–142
14. MacQueen G, Young L, Joffe R. A review of psychosocial outcome in patients with bipolar disorder. Acta Psychiatr Scand 2001;103:163–170
15. Hirschfeld RMA, Bowden C, Gitlin M, et al. Practice Guideline for the Treatment of Patients With Bipolar Disorder [Revision]. Am J Psychiatry 2002;159(suppl 4):1–50
16. Calabrese JR, Bowden CL, Sachs GS. A double-blind, placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. J Clin Psychiatry 1999;60:79–88
17. Frye M, Ketter T, Kimbrell T, et al. A placebo-controlled study of lamotrigine and gabapentin monotherapy in refractory mood disorders. J Clin Psychopharmacol 2000;20:607–614
18. Obrocea G, Dunn R, Frye M, et al. Clinical predictors of response to lamotrigine and gabapentin monotherapy in refractory affective disorders. Biol Psychiatry 2002;5:253–260
19. Calabrese JR, Fatemi S, Woyshville M. Antidepressant effect of lamotrigine in rapid cycling bipolar disorder [letter]. Am J Psychiatry 1996;153: 1236
20. Calabrese JR, Bowden C, McElroy S. Spectrum of activity of lamotrigine in treatment-refractory bipolar disorder. Am J Psychiatry 1999;156: 1019–1023
21. 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
22. Burgess S, Geddes J, Hawton K, et al. Lithium for maintenance treatment of mood disorder (Cochrane Review). Cochrane Database Syst Rev 2001; 2:CD003013
23. Denicoff K, Smith-Jackson E, Disney E, et al. Comparative prophylactic efficacy of lithium, carbamazepine, and the combination in bipolar disorder. J Clin Psychiatry 1997;58:470–478
24. Lambert PA, Venaud G. Comparative study of valpromide versus lithium in the treatment of affective disorders. Nervure 1992;5:57–65
25 Hopkins HS, Gelenberg AJ. Serum lithium levels and the outcome of maintenance therapy of bipolar disorder. Bipolar Disord 2000;2:174–179
26. Bowden C, Calabrese JR, Sachs G, et al. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar 1 disorder. Arch Gen Psychiatry 2003;60:392–400
27. Calabrese JR, Bowden CL, Sachs G, et al. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. J Clin Psychiatry 2003;64: 1013–1024
28. Endicott J, Spitzer RL. A diagnostic interview: the Schedule for Affective Disorders and Schizophrenia. Arch Gen Psychiatry 1978;35:837–844
29. Prien R, Caffey E, Klett J. Prophylactic efficacy of lithium carbonate in manic-depressive illness. Arch Gen Psychiatry 1973;28:337–341
30. Prien R, Klett J, Caffey E. Lithium carbonate and imipramine in prevention of affective episodes. Arch Gen Psychiatry 1973;29:420–425
31. Perlis R, Sachs G, Lafer B, et al. Effect of abrupt change from standard to low serum levels of lithium: a reanalysis of double-blind lithium maintenance data. Am J Psychiatry 2002;159:1155–1159
32. Bowden C, Calabrese JR, McElroy S, 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