

A Placebo-Controlled 18-Month Trial of Lamotrigine and Lithium Maintenance Treatment in Recently Manic or Hypomanic Patients With Bipolar I Disorder

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Background: Lamotrigine has been shown to be an effective treatment for bipolar depression and rapid cycling in placebo-controlled clinical trials. This double-blind, placebo-controlled study was conducted to assess the efficacy and tolerability of lamotrigine and lithium compared with placebo for the prevention of relapse or recurrence of mood episodes in recently manic or hypomanic patients with bipolar I disorder.

Methods: After an 8- to 16-week open-label phase during which treatment with lamotrigine was initiated and other psychotropic drug regimens were discontinued, patients were randomized to lamotrigine (100-400 mg daily), lithium (0.8-1.1 mEq/L), or placebo as double-blind maintenance treatment for as long as 18 months.

Results: Of 349 patients who met screening criteria and entered the open-label phase, 175 met stabilization criteria and were randomized to double-blind maintenance treatment (lamotrigine, 59 patients; lithium, 46 pa-

tients; and placebo, 70 patients). Both lamotrigine and lithium were superior to placebo at prolonging the time to intervention for any mood episode (lamotrigine vs placebo, $P = .02$; lithium vs placebo, $P = .006$). Lamotrigine was superior to placebo at prolonging the time to a depressive episode ($P = .02$). Lithium was superior to placebo at prolonging the time to a manic, hypomanic, or mixed episode ($P = .006$). The most common adverse event reported for lamotrigine was headache.

Conclusions: Both lamotrigine and lithium were superior to placebo for the prevention of relapse or recurrence of mood episodes in patients with bipolar I disorder who had recently experienced a manic or hypomanic episode. The results indicate that lamotrigine is an effective, well-tolerated maintenance treatment for bipolar disorder, particularly for prophylaxis of depression.

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BIPOLAR DISORDER is a chronic, severe disease with a prevalence of approximately 1.6% for the bipolar I form and more than 3% when other forms are included.¹⁻³ Social and vocational morbidity is high, and the mortality rate from suicide is estimated to be 3 times that of the general population.^{4,5} Nine of 10 patients with an initial episode of mania experience subsequent manic, hypomanic, depressed, or mixed episodes that are characterized by significant cognitive and behavioral dysfunction as well as mood impairment.⁶ Each additional mood episode increases the risk of future recurrences and worsens the prognosis.^{7,8} Therefore, although effective treatment of acute mood episodes in bipolar disorder is important, a primary treatment objective is the prevention of subsequent mood episodes.⁹⁻¹¹

On the basis of studies conducted primarily in the 1960s and 1970s, lithium has been the cornerstone of maintenance

therapy for bipolar disorder,⁹ but its efficacy in open and blinded, randomized maintenance studies of the last 15 years has been consistently below 50%.¹⁰⁻¹³ These considerations notwithstanding, lithium is the most well-studied and established pharmacotherapy for maintenance treatment of bipolar disorder and is indicated for this use in most countries. A recent meta-analysis of 9 placebo-controlled studies ($n = 825$) of lithium as maintenance treatment for mood disorders concluded that the drug is effective in preventing the relapse of bipolar disorder, despite considerable between-study heterogeneity in results.¹⁴ However, this review also emphasized the unmet need for effective, tolerable maintenance therapy for bipolar disorder and called for additional controlled studies comparing lithium with other therapeutic options.

Lamotrigine, which has worldwide regulatory approval for the treatment of epilepsy, has also demonstrated efficacy in bipolar depression and rapid-cycling bipolar disorder as indicated by the results of

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open as well as randomized blinded, placebo-controlled studies.¹⁵⁻²⁴ Lamotrigine monotherapy was more effective than placebo on a variety of key outcome measures for depressive episodes of bipolar I disorder.¹⁵ In a second study with parallel-group and crossover components, lamotrigine monotherapy was more effective than placebo or gabapentin in the treatment of patients with bipolar and unipolar mood disorders who were refractory to or intolerant of lithium, valproate acid, or carbamazepine.²⁴

In a 6-month blinded, randomized, parallel-group study, lamotrigine was superior to placebo in time to intervention or early discontinuation for any reason in patients with rapid-cycling bipolar illness.²³ After 6 months of monotherapy, 41% of patients treated with lamotrigine compared with 26% of placebo-treated patients were stable without relapse. This study was the first randomized, double-blind demonstration of the efficacy of lamotrigine as maintenance therapy. The current randomized, double-blind, placebo-controlled study was conducted to further these observations by assessing the efficacy and tolerability of lamotrigine and the standard maintenance therapy, lithium, compared with placebo for the prevention of relapse or recurrence of mood episodes in patients with bipolar I disorder who had recently experienced a manic or hypomanic episode.

METHODS

PATIENTS

Patients aged 18 years or older with a diagnosis of bipolar I disorder were eligible for the study if they (1) were currently manic or hypomanic as defined by the *DSM-IV*²⁵ or (2) had been manic or hypomanic within 60 days of the screening visit, had manic or hypomanic symptoms at enrollment, and had at least 1 additional manic or hypomanic episode and 1 depressed episode (including those of a mixed episode meeting *DSM-IV* criteria) within 3 years of enrollment. Patients were excluded if they had experienced more than 6 *DSM-IV* manic, hypomanic, mixed, or depressive episodes in the year prior to enrollment; had a *DSM-IV* diagnosis of or had received treatment within the year prior to enrollment for panic disorder, obsessive-compulsive disorder, social phobia, or bulimia nervosa; had a history of or current epilepsy; had clinically significant cardiac, renal, hepatic, neoplastic, or cerebrovascular disease; or were actively suicidal or had a score of 3 or more on item 3 of the 31-item Hamilton Rating Scale for Depression (HAM-D).²⁶ All patients provided written informed consent prior to study participation.

PROCEDURES

The protocol for this randomized, double-blind, parallel-group, placebo-controlled, multicenter study conducted at 64 centers (Glaxo Wellcome protocol SCAB2006, GW606) was approved by an institutional review board or ethics committee at each study site. The study included a screening phase of up to 2 weeks, an 8- to 16-week open-label phase during which lamotrigine was initiated as adjunctive therapy or monotherapy and other psychotropic drugs were discontinued, and a 76-week double-blind phase during which patients received lamotrigine, lithium, or placebo as maintenance therapy. Patients could be discontinued from any phase of the study for reasons including poor tolerance of study medication, lack of efficacy, pregnancy, investigator's or patient's unwillingness to continue the study for any reason, and noncompliance with study proce-

dures. Patients experiencing a rash of unknown origin while taking lamotrigine or undergoing double-blind therapy were to be discontinued from the study regardless of the severity of the rash.

Screening Phase

The screening phase occurred within 2 weeks after the patient's entry into the open-label phase. During this phase, psychiatric and medical histories were obtained; physical examinations including clinical laboratory tests were performed; and scores on psychiatric rating scales, including the Mania Rating Scale (MRS) from the Schedule of Affective Disorders and Schizophrenia, change version,²⁷ the HAM-D,²⁶ the Clinical Global Impressions-Severity and -Improvement scales (CGI-S and CGI-I),²⁸ and the Global Assessment Scale (GAS),²⁹ were recorded. Patients eligible by inclusion and exclusion criteria were enrolled in the open-label phase.

Open-Label Phase

During the 8- to 16-week open-label phase, all patients received open-label lamotrigine (target dosage, 200 mg/d; minimum dosage, 100 mg/d) as adjunctive therapy or monotherapy. When used as monotherapy, patients began a 6-week titration of lamotrigine to a target dosage of 200 mg/d (weeks 1-2, 25 mg/d; weeks 3-4, 50 mg/d; week 5, 100 mg/d; and week 6, 200 mg/d). When used as adjunctive therapy with valproate, the lamotrigine starting, minimum, and target dosages and the rate of titration were halved. When used as adjunctive therapy with carbamazepine, the lamotrigine starting, minimum, and target dosages and the rate of titration were doubled. In both cases, these concomitant antiepileptic drugs were gradually withdrawn so that lamotrigine monotherapy at target dosages was received for at least 1 week before the double-blind phase, with the lamotrigine dosage immediately doubled after discontinuation of valproate and gradually halved after discontinuation of carbamazepine.

Concomitant antiepileptic drugs and other psychotropic medications were permitted during the open-label phase as needed to treat an ongoing manic or hypomanic episode but were discontinued a minimum of 1 week (for oral antipsychotics, selective serotonin reuptake inhibitors, tricyclic antidepressants, lithium, and benzodiazepines) to 2 weeks (for anticonvulsants, monoamine oxidase inhibitors, and reversible monoamine oxidase inhibitors) before entry into the double-blind phase. For patients receiving lithium during the open-label phase, the dosage was tapered over at least 3 weeks and discontinued a minimum of 1 week before they entered the double-blind phase of the study.

Clinic visits were scheduled to occur weekly (or as necessary to ensure appropriate patient care) during the open-label phase. At each clinic visit, psychiatric evaluations from the screening visit were administered again, and patients were queried regarding the occurrence of adverse events, defined as any untoward medical occurrence, regardless of its suspected cause. Beginning at week 8 of the open-label phase, patients who had reached a stable dose of lamotrigine and met the criterion for response, defined as a CGI-S scale score of 3 or less maintained for at least 4 continuous weeks, were eligible to enroll in the double-blind phase of the study. Patients not meeting the criterion for response to lamotrigine at the end of 16 weeks of open-label treatment were discontinued from the study.

Double-Blind Phase

Patients who responded to treatment with lamotrigine during the open-label phase of the study were randomized 1:1:1 to receive double-blind treatment with lamotrigine (100-400 mg/d, depending on clinical response; starting dosage, 200 mg/d),

lithium (titrated to serum levels of 0.8-1.1 mEq/L), or placebo for up to 76 weeks. Psychotropic drugs other than study medication were not permitted during the double-blind phase, with the exception of short-term, intermittent use of chloral hydrate, lorazepam, temazepam, or oxazepam at low doses as needed for control of agitation, irritability, restlessness, insomnia, or hostile behavior. In the event of a mood episode, antidepressants, antipsychotics, benzodiazepines, anticonvulsants and mood stabilizers, or electroconvulsive therapy were administered as treatment intervention, the primary study end point.

Clinic visits were scheduled to occur weekly during the first 4 weeks of the double-blind phase, biweekly through week 8, and every 4 weeks thereafter, through week 76. At each clinic visit, psychiatric evaluations from the screening visit were administered again, and patients were queried regarding the occurrence of adverse events. At the week 52 clinic visit, patients were evaluated to determine whether they should continue the study. Those who had not experienced a relapse or recurrent mood episode could proceed with double-blind treatment for an additional 6 months (through week 76); those who had been treated for a relapse or recurrence during double-blind treatment through week 52 were discontinued from the study.

Two modifications in the planned study design occurred to deal with a rate of enrollment that was substantially slower than planned. Approximately midway through the study, the lithium arm was closed to enrollment in order to divert new patients into the treatments of primary interest, lamotrigine and placebo. Subsequently, the study was terminated prior to enrollment of the full planned complement of patients (100 per group). No interim analyses or other type of unblinding were used in reaching these administrative decisions.

OUTCOME MEASURES AND DATA ANALYSIS

Efficacy

The primary efficacy end point was the time to intervention (addition of pharmacotherapy or electroconvulsive therapy) for any mood episode. Secondary efficacy measures included time to early discontinuation for any reason (ie, survival in study); time to intervention for a manic, hypomanic, or mixed episode; time to intervention for a depressive episode; and mean change from baseline (defined as day 1 of the double-blind phase) in scores on the MRS, HAM-D, CGI, and GAS scales during double-blind treatment.

For statistical analyses, the efficacy population comprised all patients randomized to treatment during the double-blind phase who received at least 1 dose of study medication and provided at least 1 postbaseline primary outcome assessment.

Kaplan-Meier survival curves were generated for the time-to-event data, and differences among treatment groups were compared using log-rank tests at an $\alpha = .05$ level of significance. Patients discontinuing from the study for reasons other than the defined events for the analysis were censored at the time of drop out. For the analysis of survival in the study, all patients discontinuing prematurely for any reason except termination of the study by the sponsor were categorized as treatment failures, as were patients who had intervention for any mood episode. Patients who were discontinued due to termination of the study by the sponsor were censored from all analyses at the point of their discontinuation.

Mean change scores for the psychiatric evaluations between groups were examined with repeated-measures analysis using generalized estimating equations at an $\alpha = .05$ level of significance using observed, last observation carried forward, and mean change data. For the latter analysis, the mean of all observed data was applied to missing values. Results for all 3 analyses were similar. Mean change data are reported here. Cat-

egorical variables were analyzed using the Fisher exact test. No interim analyses were performed on any of the study end points. No adjustments for multiple comparisons were applied.

Safety

The incidence of adverse events was summarized for each phase of the study for all patients who had received at least 1 dose of study medication during that phase. Laboratory and vital signs data were analyzed for frequency of clinically significant shifts.

Statistical Power

Projected sample sizes were based on the number of patients deemed necessary to detect differences between the lamotrigine group and the placebo group in the incidence of relapse or recurrence of a manic episode during the double-blind phase. It was estimated that a minimum of 62 patients per group was required to detect an incidence of relapse or recurrence of a manic episode of 65% for placebo and 40% for lamotrigine at a power of 80% and an α of .05.

RESULTS

PATIENTS

Of 349 patients enrolled in the open-label phase, 175 were randomized to maintenance treatment during the double-blind phase (lamotrigine, 59 patients; lithium, 46 patients; and placebo, 70 patients) (**Table 1**). One patient each in the lamotrigine and placebo groups had no postbaseline assessments following entry into the double-blind phase of the study and was excluded from all further efficacy and safety analyses. Two patients in the lithium group did not provide any postbaseline efficacy assessments following entry in the double-blind phase of the study and were excluded from all further efficacy analyses. The lithium sample size was smallest due to truncation of this arm partway through the study. Because some study centers did not randomize complete blocks ($n = 6$) of study medication, the sample sizes for lamotrigine and placebo were unequal.

The most common reason that patients in the open-label phase were not randomized to the double-blind phase was the occurrence of adverse events (12%). Of the 175 patients who entered the double-blind phase, 35 patients were discontinued prematurely because of early termination of the study by the sponsor. The mean (SD) length of time these patients spent in the study was 300 (115) days (range, 136-582 days). For the remaining patients, the most common reasons for discontinuation from the study, other than intervention for a mood episode, were adverse events for the lithium group (24%; $P = .01$ vs placebo; $P = .003$ vs lamotrigine) and withdrawal of consent for the lamotrigine group (7%).

Demographic characteristics and psychiatric history of patients enrolled in the double-blind phase are summarized in **Table 2**. The patient sample enrolled in the study had a mean age in the early 40s and was approximately equally divided between men and women. Nearly all patients had previously received medication for mood-related disturbance, and roughly two thirds required psychiatric hospitalization at some point. Overall demographic and disease characteristics of the sample were comparable

Table 1. Patient Disposition*

Category	Open-Label Phase (n = 349)†	Double-blind Phase (n = 175)‡		
		Lamotrigine (n = 59)	Lithium (n = 46)	Placebo (n = 70)
Completed study phase	184 (53)	3 (5)	1 (2)	0 (0)
Discontinued study prematurely				
Failed to meet randomization criteria	25 (7)	NA	NA	NA
Adverse event	42 (12)	3 (5)	11 (24)§	3 (4)
Consent withdrawn	29 (8)	4 (7)	2 (4)	3 (4)
Lost to follow-up	30 (9)	1 (2)	3 (7)	1 (1)
Protocol violation	9 (3)	2 (3)	1 (2)	1 (1)
Other	30 (9)	3 (5)	1 (2)	2 (3)
Termination due to study discontinuation	NA	15 (25)	9 (20)	11 (16)
Intervention for a mood episode	NA	28 (47)	18 (39)	49 (70)

Abbreviation: NA, not applicable.

*Data are given as the number (percentage) of patients.

†Two patients in the open-label phase did not provide any postscreening assessments and were excluded from further analyses.

‡One patient each in the lamotrigine and placebo groups did not provide any postbaseline assessments and were excluded from subsequent efficacy and safety analyses. Two patients in the lithium group did not provide any postbaseline efficacy assessments and were excluded from subsequent efficacy analyses.

§Lithium vs placebo, $P = .01$; lithium vs lamotrigine, $P = .01$.

||Patients terminated due to study discontinuation were censored from efficacy analyses at the point of discontinuation.

Table 2. Patient Demographic and Disease Characteristics

Characteristic	Open-Label Phase (n = 347)	Double-blind Phase (n = 173)		
		Lamotrigine (n = 58)	Lithium (n = 46)	Placebo (n = 69)
Demographic				
Age, mean (SD), y	40.7 (11.8)	40.6 (12.6)	41.9 (11.3)	40.9 (11.0)
Male sex, No. (%)	172 (50)	26 (45)	22 (48)	34 (49)
Weight, mean (SD), kg	78.1 (16.8)	78.7 (17.7)	79.9 (19.2)	79.0 (17.2)
Illness characteristics and treatment history				
History of psychotic episodes, No. (%)*	160 (46)	22 (38)	21 (46)	28 (41)
Ever hospitalized for mood-related disturbances, No. (%)*	230 (66)	35 (60)	31 (67)	42 (61)
Ever attempted suicide, No. (%)*	102 (29)	16 (28)	19 (41)‡	13 (19)
Age of first depression, mean (SD), y	23.4 (12.1)	25.3 (12.8)	24.6 (12.3)	22.4 (11.7)
Age of first mania or mixed episode, mean (SD), y	26.0 (11.8)	26.7 (11.3)	29.7 (13.8)	24.1 (9.9)
No. of mood episodes in past year, mean (SD)				
Depression	1.0 (0.8)	0.9 (0.6)	1.0 (0.9)	1.0 (0.8)
Mania	1.4 (0.8)	1.3 (0.8)	1.3 (0.7)	1.6 (0.9)
Hypomania	0.3 (0.6)	0.2 (0.5)	0.4 (0.6)	0.3 (0.7)
Mixed	0.2 (0.5)	0.2 (0.5)	0.2 (0.5)	0.2 (0.7)
Psychotropic medication use, No. (%)†				
At least 1 prior treatment	327 (94)	53 (91)	44 (96)	63 (91)
Valproate	147 (45)	26 (49)	10 (23)§	32 (51)
Carbamazepine	94 (29)	12 (23)	13 (30)	18 (29)
Lithium	225 (69)	38 (72)	31 (70)	42 (67)
Antidepressants	185 (57)	29 (55)	26 (59)	40 (63)
Antipsychotics	193 (59)	30 (57)	24 (55)	36 (57)
Benzodiazepines	176 (54)	28 (53)	23 (52)	33 (52)
Duration of index mania or hypomania, No. (%)				
1-4 wk	161 (46)	24 (41)	20 (43)	31 (45)
>4-8 wk	94 (27)	14 (24)	15 (33)	18 (26)
>8-24 wk	73 (21)	14 (24)	10 (22)	15 (22)
>24 wk	18 (5)	6 (10)	1 (2)	4 (6)
Missing	1 (<1)	0 (0)	0 (0)	1 (1)
MRS score at screening, mean (SD)	22.9 (6.7)	22.3 (6.8)	22.3 (5.6)	22.4 (7.8)
17-Item HAM-D score at screening, mean (SD)	7.6 (5.4)	7.7 (5.9)	6.7 (4.5)	6.9 (5.4)
CGI-S scale score at screening, mean (SD)	4.3 (0.8)	4.3 (0.6)	4.1 (0.7)	4.3 (1.0)
GAS score at screening, mean (SD)	48.8 (11.8)	47.6 (11.5)	49.3 (12.0)	48.4 (12.3)

Abbreviations: CGI-S, Clinical Global Impressions–Severity; GAS, Global Assessment Scale; HAM-D, Hamilton Rating Scale for Depression; MRS, Mania Rating Scale.

*Remaining patients either were negative for presence of the parameter or had missing data.

†Data are missing for some patients.

‡Lithium vs placebo, $P = .01$.

§Lithium vs placebo, $P = .005$; lithium vs lamotrigine, $P = .01$.

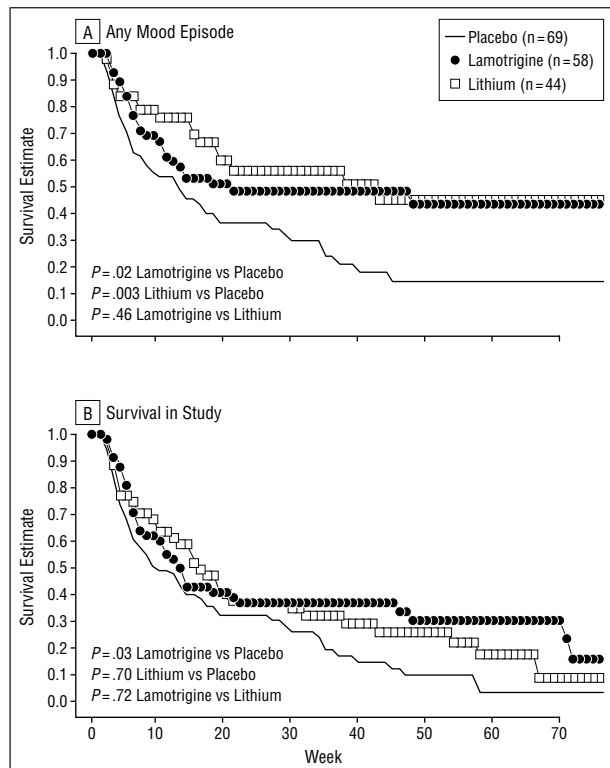


Figure 1. Kaplan-Meier survival curves for time to intervention for any mood episode (A) or discontinuation from the study (B).

across the 3 treatment groups, with 2 exceptions. A history of previous suicide attempt was more frequent in the lithium group (41%) compared with the placebo group (19%) ($P=.01$). Among patients who had previously received at least 1 psychotropic medication, fewer patients had previously been treated with valproate in the lithium group (23%) compared with the placebo group (51%) ($P=.005$) or the lamotrigine group (49%) ($P=.01$).

In addition to lamotrigine, other psychiatric medications were allowed during the initial part of the open-label phase and were used by 78% of all patients and 75% of those eventually randomized. Medications used by 10% or more of all patients were lithium (18%), lorazepam (18%), clonazepam (15%), valproate (14%), and haloperidol (14%). These percentages were only slightly lower for patients who were eventually randomized, except for clonazepam (9%) and haloperidol (9%), and were comparably distributed among the double-blind treatment groups. Of 349 patients who entered the initial open-label phase of the study, 175 (50%) achieved stabilization criteria and entered the double-blind phase of the study.

TIME TO ANY MOOD EPISODE

Both lamotrigine and lithium were significantly superior to placebo on time to intervention for any mood episode (lamotrigine vs placebo, $P=.02$; lithium vs placebo, $P=.003$) (**Figure 1A**). Lamotrigine and lithium did not differ from each other on this parameter ($P=.46$). Median survival times are provided in **Table 3**. Medications added at the point of intervention included antidepressants ($n=19$ patients), lamotrigine ($n=19$), atypical antipsychotics ($n=16$), ben-

zodiazepines ($n=14$), atypical antipsychotics ($n=9$), valproate ($n=6$), lithium ($n=3$), and carbamazepine ($n=1$). The distribution of medications used as treatment interventions was comparable across the 3 treatment groups.

In the analysis of overall survival in the study (ie, categorizing all early discontinuations as events), lamotrigine was superior to placebo (lamotrigine vs placebo, $P=.03$; lithium vs placebo, $P=.07$) (**Figure 1B**). Lamotrigine and lithium did not differ from each other on this parameter ($P=.72$). In the placebo group, 11 (16%) of 69 patients completed the study or were terminated from the protocol because of study discontinuation vs 18 (31%) of 58 in the lamotrigine group ($P=.05$) and 10 (23%) of 44 in the lithium group ($P=.27$).

INCIDENCE OF AND TIME TO MOOD EPISODES

Among patients experiencing mood episodes that required intervention during the double-blind phase, episodes of elevated mood (mania, hypomania, and mixed states) were more frequent than depressive episodes for the lamotrigine and placebo groups. Thus, of 28 interventions for mood episodes among patients in the lamotrigine group, 20 (71%) were for mood elevation (mania, 11; hypomania, 5; and mixed, 4), and 8 (29%) were for depression. Of 49 interventions among placebo patients, 28 (57%) were for mood elevation (mania, 13; hypomania, 9; and mixed, 6), and 21 (43%) were for depression. In contrast, depressive episodes constituted a majority of events requiring intervention for the lithium group. Of 18 interventions among patients in the lithium group, 10 (56%) were for depression, and 8 (44%) were for mood elevation (mania, 4; hypomania, 2; and mixed, 2).

Lamotrigine, but not lithium, was superior to placebo at prolonging the time to a depressive episode (lamotrigine vs placebo, $P=.02$; lithium vs placebo, $P=.17$) (**Figure 2A**). Lamotrigine and lithium did not differ from each other on this parameter ($P=.36$).

Lithium, but not lamotrigine, was superior to placebo at prolonging the time to a manic, hypomanic, or mixed episode (lithium vs placebo, $P=.006$; lamotrigine vs placebo, $P=.28$) (**Figure 2B**). A trend favored lithium over lamotrigine on this parameter ($P=.09$).

CHANGES IN SYMPTOM SEVERITY AND OVERALL FUNCTIONING

Change from baseline scores for the HAM-D indicated lesser overall degrees of worsening with lamotrigine compared with placebo (**Table 4**). Change scores in the lithium group did not differ from those in the placebo or lamotrigine groups for these evaluations. Conversely, change from baseline scores for the MRS indicated lesser overall degrees of worsening with lithium compared with placebo and lamotrigine. There were no overall differences between any of the treatment groups for CGI scale or GAS scores.

A regression of individual patient end point changes in the MRS vs the HAM-D indicated a marginally significant positive relationship for the lamotrigine group only (lamotrigine: mean [SE], 0.41 [0.21]; $r^2=0.06$; $P=.06$; lithium: mean [SE], -0.02 [0.11]; $r^2=0.001$; $P=.82$; and placebo: mean [SE], -0.12 [0.14]; $r^2=0.01$; $P=.40$).

Table 3. Median Survival Data

	Lamotrigine (n = 58)	P Value vs Placebo	Lithium (n = 44)	P Value vs Placebo	Placebo (n = 69)
Survival in study					
Survival, median (95% CL), d	85 (44, 142)	.03	101 (59, 202)	.07	58 (34, 108)
No. of events	40		34		58
Time to intervention					
Mood episode					
Survival, median (95% CL), d	141 (71, >547)	.02	292 (123, >547)	.003	85 (37, 121)
No. of events	28		18		49
Mania					
Survival, median (95% CL), d	NE	.28	NE	.006	203 (108, >547)
No. of events	20		8		28
Depression					
Survival, median (95% CL), d	NE	.02	NE	.17	269 (183, >547)
No. of events	8		10		21

Abbreviations: CL, confidence limits; NE, not evaluable when probability of survival fails to reach 50%.

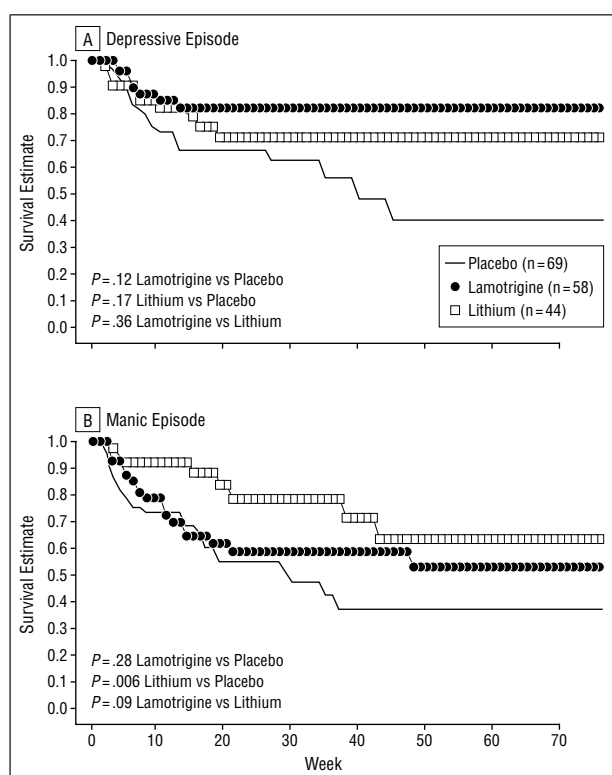


Figure 2. Kaplan-Meier survival curves for time to intervention for a depressive episode (A) or a manic, hypomanic, or mixed episode (B).

ADVERSE EVENTS

The most common treatment-emergent adverse event occurring during the open-label or double-blind phases was headache (**Table 5**). During the double-blind phase of the study, the incidence of headache was significantly higher in the lamotrigine group compared with the lithium group. The incidence of diarrhea was significantly higher in the lithium group compared with the lamotrigine group. Most adverse events were considered to be mild or moderate and resolved without sequelae, regardless of the study phase. A 54-year-old female patient developed a moderately severe maculopapular, nonpruritic rash during the open-label phase, and it resolved uneventfully fol-

Table 4. Change From Baseline Scores on Psychiatric Rating Scales During the Double-Blind Study Phase*

Scale	Lamotrigine (n = 58)	Lithium (n = 44)	Placebo (n = 69)
MRS	1.79 (5.67)	-0.04 (2.75)†	2.35 (5.03)
HAM-D	2.05 (3.38)‡	2.68 (4.99)	3.92 (6.01)
GAS	-3.19 (11.89)	-3.85 (9.89)	-5.63 (9.27)
CGI-Severity	0.37 (0.74)	0.44 (0.77)	0.56 (0.82)
CGI-Improvement	0.79 (1.11)	0.84 (1.17)	0.95 (1.16)

Abbreviations: CGI, Clinical Global Impressions; GAS, Global Assessment Scale; HAM-D, Hamilton Rating Scale for Depression; MRS, Mania Rating Scale.

*Data are given as mean (SD).
 †Lithium vs placebo, P = .001; lithium vs lamotrigine, P = .03 (repeated measures analysis on all postbaseline data).
 ‡Lamotrigine vs placebo, P = .03 (repeated measures analysis on all postbaseline data).

Table 5. Common Adverse Events Reported During the Open-Label and Double-blind Phases*

Adverse Event	Open-Label Phase (n = 347)	Double-blind Phase (n = 173)		
		Lamotrigine (n = 59)	Lithium (n = 46)	Placebo (n = 69)
Headache	86 (25)	12 (20)†	2 (4)	11 (16)
Any rash	38 (11)	2 (3)	4 (9)	6 (9)
Infection	34 (10)	8 (14)	5 (11)	10 (14)
Somnolence	34 (10)	5 (8)	6 (13)	6 (9)
Nausea	35 (10)	4 (7)	9 (20)	6 (9)
Diarrhea	32 (9)	3 (5)	13 (28)‡	6 (9)
Insomnia	29 (8)	5 (8)	6 (13)	4 (6)
Influenza	14 (4)	6 (10)	3 (7)	4 (6)

*Adverse events occurring in at least 10% of patients during the open-label or double-blind phase are listed. Data are given as the number (percentage) of patients.
 †Lamotrigine vs lithium, P = .02.
 ‡Lithium vs lamotrigine, P = .002; lithium vs placebo, P = .009.

lowing hospitalization and discontinuation of lamotrigine. There were no cases of serious rash during the double-blind phase of the study.

Adverse events led to the withdrawal of 42 patients from the open-label phase and 16 patients from the double-blind phase (placebo, 3 patients; lamotrigine, 3 patients; and lithium, 11 patients) (lithium vs placebo, $P = .01$; lithium vs lamotrigine, $P = .003$). The most frequent adverse events leading to withdrawal from the open-label phase were rash (17 cases; 5% of patients) and mania (12 cases; 3%). The most frequent adverse events leading to withdrawal from the double-blind phase were mania (placebo, 2 patients; lithium, 2 patients; and lamotrigine, 2 patients), somnolence (lithium, 2; lamotrigine, 1), depression (placebo, 1; lithium, 2), diarrhea (placebo, 1; lithium, 4) (lithium vs lamotrigine, $P = .04$), nausea (lithium, 5) (lithium vs lamotrigine, $P = .02$; lithium vs placebo, $P = .009$), and rash (placebo, 2; lithium, 2).

The incidence of laboratory values not within reference ranges and/or clinically significant changes from normal was low and did not suggest an effect of either of the active treatments, except for an increase in the number of lithium patients with elevated thyroid-stimulating hormone levels (prospectively defined as > 4.67 mIU/L). In this group, final postbaseline assessments for 7 (18%) of 38 patients were elevated compared with 1 (2%) of 60 placebo patients and 0 lamotrigine patients. Also as expected, the mean total white blood cell count increased in patients receiving lithium compared with placebo. The incidence of patients with a 7% or greater increase in body weight during the double-blind phase of the study was 11%, 10%, and 2% for the lamotrigine, lithium, and placebo groups, respectively.

One patient in the lamotrigine group, a 47-year-old woman, attempted suicide 24 days into the double-blind phase of the study by taking an overdose of study medication after reporting auditory hallucinations and hearing voices that told her to kill herself. She recovered uneventfully following gastric lavage and hospitalization for several days. In the treating psychiatrist's opinion, the events were not reasonably attributable to the study medication.

The number of patients in each treatment group who ever had a score of 3 or greater on HAM-D item 3 (suicidality) during the double-blind phase did not differ significantly between any of the treatment groups (lamotrigine, 2; lithium, 0; and placebo, 2).

COMMENT

In this double-blind comparison of lamotrigine and lithium monotherapy vs placebo in the maintenance treatment of recently manic or hypomanic patients with bipolar I disorder, both lamotrigine and lithium were more effective than placebo at prolonging the time to any mood episode, which was the primary efficacy end point of the study. In a previous large maintenance-therapy study, significantly fewer patients with rapid-cycling bipolar disorder relapsed during 6 months of therapy with lamotrigine compared with placebo.²³ These 2 studies provide strong evidence for the efficacy of lamotrigine in preventing the relapse and recurrence of bipolar illness.

These results also extend the accumulating evidence of the efficacy of lamotrigine administered either acutely or long-term in controlling depressive symptoms

of bipolar disorder.^{15,16,23,24,30} In this study, lamotrigine was superior to placebo at prolonging the time to intervention for a depressive episode. In addition, lamotrigine improved scores compared with placebo on psychiatric evaluations of depressive symptoms (HAM-D). Considering the morbidity, mortality, and overall burden associated with the depressive phase of the illness,³¹ lamotrigine appears to provide a complementary benefit to other drugs used in the treatment of bipolar disorder.

This study does not suggest that lamotrigine is effective for preventing relapse or recurrence of manic symptoms. Lamotrigine was not statistically superior to placebo at prolonging the time to a manic, hypomanic, or mixed episode and did not significantly improve scores compared with placebo on the psychiatric evaluation of manic symptoms (MRS). However, regression analysis changes in the HAM-D and MRS scores of individual patients did suggest that, for patients in the lamotrigine group, there was a positive correlation between the degree of protection against return of depression and manic symptoms. Moreover, compared with placebo, there was no evidence in this study that manic symptoms worsened during lamotrigine treatment.

This is the first study in a bipolar I population in which lithium differentiated from placebo using modern survival analytic methods, and it arguably provides some of the strongest evidence available for the efficacy of lithium in maintenance treatment of bipolar disorder. Along with the study of Bowden et al,³² it provides the only placebo-controlled data in which lithium taken during open-phase treatment was tapered at the point of randomization, avoiding abrupt withdrawal-induced relapse on placebo. In line with the results of the current study, Bowden et al reported a nonsignificant extension of time to 25% relapse with mania among lithium-treated, compared with placebo-treated, patients (293 days vs 189 days) but did not suggest that lithium was efficacious in delaying the relapse time to depression. Few other maintenance studies of treatments for bipolar disorder have separately analyzed relapse of manic and depressive episodes. The studies of Dunner et al³³ and Denicoff et al³⁴ also suggest that lithium has maintenance efficacy for manic, but not depressive, dimensions of bipolar disorder. Because the number of lithium-treated patients in the current study was smaller than originally planned, the results of lithium treatment reported here should be interpreted with caution.

This study is one of few placebo-controlled trials that provides a direct comparison of the efficacy of 2 or more medications for the prevention of relapse and recurrence of bipolar illness. The anticonvulsant carbamazepine has been compared with lithium in several maintenance-therapy studies lacking a placebo control group.^{10,35-37} Most of these studies demonstrate that carbamazepine is less effective than lithium. Lithium has also been compared with valproate in a large placebo-controlled maintenance-therapy study.³² In the latter study, valproate was not more effective than placebo or lithium in preventing or forestalling recurrence of manic or depressive episodes, although valproate was significantly more effective than placebo or lithium in preventing the recurrence of mood episodes severe enough to prompt patients' discontinuation from the study.

The Lamictal 606 Study Group

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Lamotrigine was well-tolerated and had an adverse-event profile consistent with other studies of bipolar disorder¹⁵⁻²⁴ as well as epilepsy.³⁰ The incidence of discontinuations because of adverse events and the incidence of several of the most common adverse events were lower with lamotrigine than with lithium. The relative tolerability of lamotrigine compared with lithium was also indicated in the analysis of survival in the study, which captures the contribution of tolerability to patients' longevity in the study. Lamotrigine was superior to placebo in prolonging overall survival in the study when all discontinuations were considered treatment failures, but lithium was not.

This study has both strengths and weaknesses. It employed a classic enriched maintenance design that is used in most maintenance studies in psychiatry. Enriched designs decrease variance in the population of patients randomized to double-blind treatment and, for this reason, have been commonly employed in previously conducted lithium maintenance studies. By using an open-label treatment period to exclude patients who respond poorly or fail to tolerate study medication, a more homogeneous population is randomized to double-blind therapy, and, potentially, fewer patients are subjected to placebo treatment. The relative homogeneity of the patient populations facilitates detection of treatment-attributed responses but may limit generalizability.

This is the first placebo-controlled study to follow up bipolar patients for as long as 18 months. The longer duration provided clinical and statistical advantages, the latter via increased power of the survival analyses owing to the observation of more events and less frequent censoring. A potential disadvantage of longer periods of study is that if attrition is nonrandom, then time-to-event analyses will be skewed, a potential bias that may be handled by considering all early discontinuations as events in the time-to-event analysis. This has justification in bipolar dis-

order studies, as it does in studies of certain other disease states, because failure to stay in treatment is associated with adverse social, financial, clinical, and mood episode consequences.³⁸⁻⁴² Overall survival, or discontinuation from the study for any reason, may provide a more clinically relevant measure of overall treatment effectiveness than time to intervention for a mood episode in maintenance studies of bipolar disorder. Moreover, consistency of findings across complementary imputation methods, as we report here, reinforces the strength of the results. The 18-month study period also allows for the detection of differences that emerged later, in this case the recognition of the relatively late-occurring and cumulative advantage of lamotrigine compared with placebo. Had this study been of 6 months' duration, these 2 fundamental advantages would have been lost.

The limitation of the study to patients who had experienced a recent manic or hypomanic episode may have tended to increase the proportion of manic relapses in all groups. A similarly designed study that enrolled patients with a recent episode of depression is nearing completion. Maintenance studies with placebo monotherapy arms also tend to enroll somewhat less severely ill bipolar I patients with less comorbidity than is seen in epidemiological studies.^{32,35,43} However, the characteristics of the population enrolled in this study (eg, two thirds with previous psychiatric hospitalization and one fourth with a history of attempted suicide) suggest at least a moderately ill population.

In the aggregate, our results indicate that lamotrigine was as effective as lithium, with each drug having a relatively specific profile of benefits and limitations in terms of efficacy. The results complement the growing body of evidence demonstrating the utility of lamotrigine in acute and maintenance treatment of bipolar disorder.

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Correction

Errors in Text, Figures, and Table. In the article titled “A Placebo-Controlled 18-Month Trial of Lamotrigine and Lithium Maintenance Treatment in Recently Manic or Hypomanic Patients With Bipolar I Disorder,” published in the April 2003 issue of the ARCHIVES (2003;60:392-400), the last line of the first paragraph on page 393 should have read “In a second study with parallel-group and crossover components, lamotrigine monotherapy was more effective than placebo or gabapentin in the treatment of patients with bipolar and unipolar mood disorders who were refractory to or intolerant of lithium, valproic acid, or carbamazepine.²⁴”; the *P* value in Figure 1B for Lithium vs Placebo on page 396 should have read *P* = .07; the *P* value in Figure 2A for Lamotrigine vs Placebo on page 397 should have read *P* = .02; and the table heading in Table 5 on page 397 should have read Lamotrigine (n = 58). The ARCHIVES regrets the errors.