A Double-Blind, Placebo-Controlled, Prophylaxis Study of Lamotrigine in Rapid-Cycling Bipolar Disorder

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Background: Patients with rapid-cycling bipolar disorder are often treatment refractory. This study examined lamotrigine as maintenance monotherapy for rapid-cycling bipolar disorder.

Method: Lamotrigine was added to patients' current psychotropic regimens and titrated to clinical effect during an open-label treatment phase. Stabilized patients were tapered off other psychotropics and randomly assigned to lamotrigine or placebo monotherapy for 6 months. Time to additional pharmacotherapy for emerging symptoms was the primary outcome measure. Secondary efficacy measures included survival in study (time to any premature discontinuation), percentage of patients stable without relapse for 6 months, and changes in the Global Assessment Scale and Clinical Global Impressions-Severity scale. Safety was assessed from adverse event, physical examination, and laboratory data.

Results: 324 patients with rapid-cycling bipolar disorder (DSM-IV criteria) received open-label lamotrigine, and 182 patients were randomly assigned to the double-blind maintenance phase. The difference between the treatment groups in time to additional pharmacotherapy did not achieve statistical significance in the overall efficacy population. However, survival in study was statistically different between the treatment groups ($p = .036$). Analyses also indicated a 6-week difference in median survival time favoring lamotrigine. Forty-one percent of lamotrigine patients versus 26% of placebo patients ($p = .03$) were stable without relapse for 6 months of monotherapy. Lamotrigine was well tolerated; there were no treatment-related changes in laboratory parameters, vital signs, or body weight. No serious rashes occurred.

Conclusion: This was the largest and only prospective placebo-controlled study of rapid-cycling bipolar disorder patients to date; results indicate lamotrigine monotherapy is a useful treatment for some patients with rapid-cycling bipolar disorder.

(J Clin Psychiatry 2000;61:841–850)

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Supported by a grant from Glaxo Wellcome Inc., Research Triangle Park, N.C. For further disclosure information, see end of article.

Presented in part at the 153rd annual meeting of the American Psychiatric Association, May 17, 2000, Chicago, Ill.; the 22nd annual Collegium Internationale Neuropsychopharmacologicum, July 9–13, 2000, Brussels, Belgium; and the Second European Stanley Foundation Conference on Bipolar Disorder, August 2000, Amsterdam, the Netherlands.

The authors thank Robert Post, M.D., and Gabrielle Leverich, M.S.W., of the National Institute of Mental Health for their assistance in the design and analysis of this study; the Glaxo Wellcome Neurology and Psychiatry Clinical Statistics Section for their statistical analysis of the data; and Gary Evoniuk, Ph.D., and Tracey Fine, M.Sc., for assistance in the preparation of this article.

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Emil Kraepelin[1] first described frequent affective cycling associated with manic depressive insanity in his landmark textbook. He documented bipolar patients who exhibited episodes in excess of 4 per year, a minimum frequency later included in the earliest conceptualizations of this variant of the illness by Dunner and Fieve.[2] Subsequent studies have validated the concept of rapid cycling.[3,4] The rapid-cycling variant of bipolar disorder appears to account for 14% to 53% of patients who have bipolar disorder.[2,4–7] The prevalence rate of this subtype was reported to be as low as 4% in bipolar I disorder and as high as 31% in bipolar II disorder in one study,[6] but did not differ in another.[7] Seventy-two percent to 82% of these patients exhibited poor response to lithium.[2,5] For example, in a 5-year prospective study of lithium re-

sponse, Maj and colleagues[8] noted the absence of rapid cycling in responders to lithium but an incidence rate of 26% in nonresponders.

Indeed, combination therapy has become standard in the medical management of patients with rapid-cycling bipolar disorder.[9,10] Although both divalproex and lithium are commonly used in the treatment of rapid cycling, either alone or in combination, neither has been evaluated in controlled trials in this population. The adjunctive use of marketed antidepressant medications is common in this population, but this practice may place some patients at increased risk for the development of hypomania/mania or cycle acceleration.[11,12] Therefore, a mood stabilizer that possesses documented antidepressant efficacy would be a useful treatment for rapid-cycling bipolar disorder.

Lamotrigine, an established anticonvulsant of the phenyltriazine class, was shown to have positive effects on mood during its clinical development for epilepsy.[13] More recently, several clinical studies[14–21] of patients with bipolar disorder, including some with treatment-resistant forms of depression and rapid cycling, suggested lamotrigine might have antidepressant and mood-stabilizing properties.

This study was therefore designed to examine the safety and efficacy of lamotrigine as monotherapy for the long-term prophylaxis of mood episodes in patients with rapid-cycling bipolar disorder. It is one in a series of controlled studies investigating lamotrigine for the treatment of bipolar disorder and is the first double-blind maintenance study of lamotrigine. It is also the first controlled study of any medication in a cohort of prospectively defined patients with rapid-cycling bipolar disorder.

METHOD

Patients

Patients eligible for participation were men and women, 18 years of age or older, who had a diagnosis of bipolar disorder I or II with rapid cycling as defined by *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) criteria.[22] Patients were required to be in good physical health based on medical history, physical examination, and laboratory (including thyroid function tests) and electrocardiograph (ECG) assessments conducted at screening. Patients taking thyroid replacement therapy were required to be on a stable dose for 3 months and to be biochemically euthyroid prior to study enrollment.

Patients were excluded from study participation if on clinical evaluation they had a significant DSM-IV Axis II diagnosis suggestive of likely noncompliance with study requirement or nonresponsiveness to pharmacotherapy, were actively suicidal or had a score ≥ 3 on item 3 of the 17-item Hamilton Rating Scale for Depression (HAM-D),[23] or had a DSM-IV diagnosis of panic disorder, obsessive-compulsive disorder, social phobia, or an eating disorder within the previous year. Patients who had previously received treatment with lamotrigine were excluded from study participation if treatment duration had been 6 or more weeks and was within 6 months of study enrollment; if they had experienced an allergic or idiosyncratic reaction to treatment, including rash; or if lamotrigine had been received during a previous clinical study. Other exclusion criteria ruled out general medical conditions.

Study Design and Procedures

This multicenter study (Glaxo Wellcome Protocol 105-614) employed a double-blind, flexible-dose, placebo-controlled, parallel-group design. Local institutional review boards approved the study protocol and the informed consent form. Patients gave written informed consent before study participation.

The study was conducted in 2 phases beginning with the preliminary phase, an open-label, stabilization phase, and followed by a double-blind, placebo-controlled randomized phase.

Preliminary phase. Patients entered the preliminary phase either euthymic or experiencing a mood episode (manic, hypomanic, depressed, or mixed) as defined by DSM-IV criteria for bipolar disorder. After screening, patients began a 6-week titration of lamotrigine to a target dose of 200 mg/day (weeks 1–2: 25 mg/day; weeks 3–4: 50 mg/day; week 5: 100 mg/day). After week 5, lamotrigine dose increases were allowed in increments of 100 mg/week up to a maximum dose of 300 mg/day. Doses were adjusted as necessary for concomitant divalproex or carbamazepine treatment. This flexible dosing schedule allowed for a lamotrigine range of 100 to 300 mg/day, depending on tolerability at the end of the preliminary phase.

During the screening visit, results from the following assessments were obtained: the Structured Clinical Interview for DSM-IV,[24] medical and psychiatric history, physical examination, 12-lead ECG, clinical laboratory assessments, thyroid function testing, serum pregnancy test, urine drug screen, HAM-D, Mania Rating Scale (MRS) from the Schedule for Affective Disorders and Schizophrenia (SADS),[25] Clinical Global Impressions-Severity scale (CGI-S),[26] Global Assessment Scale (GAS),[27] and a retrospective life chart.[28] Clinic visits were conducted at screening (within 14 days of preliminary phase day 1), day 1 of the preliminary phase, and then weekly thereafter until randomization. The 17-item HAM-D, MRS, CGI-S, and GAS adverse event probe were conducted at each of these visits, and concomitant medication and lamotrigine dosing records were reviewed. The HAM-D and MRS were used to determine patient eligibility for randomization. During the first 4 weeks, use of additional psychotropic medications was allowed to treat acute mood episodes as clinically necessary. However, after 4 to 8 weeks of exposure to lamotrigine, all other psychotropic medications, includ-

ing lithium, were tapered provided that patients met the criteria for wellness. Randomization criteria were defined as a minimum daily dose of lamotrigine of 100 mg with a score ≤ 14 on the HAM-D and ≤ 12 on the MRS from the SADS-Change version over a 2-week period.

Patients were eligible to enter the 26-week randomized phase if they successfully completed the taper while maintaining the minimum criteria for wellness, had no change in lamotrigine dosage during the final week of the preliminary phase, and had no mood episodes requiring additional pharmacotherapy or electroconvulsive therapy (ECT) after the first 4 weeks of the preliminary phase.

Randomized phase. In the randomized phase, patients were randomly assigned in a 1:1 ratio to treatment with lamotrigine or matching placebo in a double-blind fashion. Additionally, patients were stratified by diagnosis of bipolar I or II disorder. At the start of this phase, patients immediately discontinued open-label lamotrigine and began double-blind treatment with lamotrigine or placebo. Lamotrigine and matching placebo were supplied in 100-mg dispersible tablets and administered orally once daily.

Double-blind medication dosage was also flexible during the randomized phase and varied from 100 to 500 mg/day. Patients began treatment with the same dose with which they ended the preliminary phase. If patients experienced a change of symptoms, i.e., a mood episode was emerging, the investigator could increase the dosage of the blinded study medication to the next highest dose in increments of 100 mg/week up to a maximum of 500 mg/day. If an increase in the dose of study medication was not effective or appropriate, then patients reached primary study endpoint and additional psychotropic medications could be added to study medication.

If patients did not respond to study treatment and pharmacotherapy was clinically indicated to treat emerging symptoms of a mood episode, the investigator was encouraged to add lithium or divalproex. During a prestudy start-up meeting, investigators reached consensus on the clinical presentation patients were to exhibit to determine primary study endpoint and initiate additional treatment. Based on the available literature, a decision was made to mimic clinical decision-making and intervene early, prior to the development of a full mood episode.[29] Further, the investigators agreed to treat emerging symptoms of hypomania more aggressively than they would symptoms of mild depression. Therefore, for the purpose of this study, relapse was operationally defined as the need for additional pharmacotherapy for a mood episode or one that was thought to be emerging.

The addition of divalproex necessitated immediate halving of lamotrigine or placebo dosage. In the event that lithium or divalproex was ineffective or inappropriate, the investigator could choose any regimen of pharmacotherapy or ECT. Any appropriate antipsychotic medication could be used to treat patients with psychotic symptoms. The results of these interventions will be reported in a future publication. Lorazepam (up to 2 mg/day) was allowed to control agitation, irritability, restlessness, insomnia, or hostile behavior throughout the randomized phase for patients responding to study treatment.

On day 1 of the randomized phase, patients underwent a physical examination that included weight and vital signs assessments, clinical laboratory assessments, serum pregnancy test, urine drug screen tests, plasma lamotrigine level determinations, HAM-D, MRS, CGI-S, GAS, a prospective life chart,[30] adverse event probe, and concomitant medication and lamotrigine dosing records. Randomized phase visits were conducted at weeks 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24 and included HAM-D, MRS, CGI-S, and GAS, and review of the prospective daily life chart, the adverse event probe, and concomitant medication and lamotrigine dosing records. Patients who completed week 26 or discontinued prematurely repeated all assessments performed on day 1 of the randomized phase.

Data Analysis

Efficacy. The intent-to-treat (ITT) population included all patients who were randomly assigned to study treatment in the randomized phase. The primary outcome analyses for the randomized phase included all patients who received at least 1 dose of study drug, had at least 1 postbaseline primary outcome assessment during the randomized phase, or required additional therapy for symptoms of an emerging mood episode.

The primary outcome measure was time to additional pharmacotherapy for emerging mood symptoms. Another measure of overall efficacy was survival in study. Kaplan-Meier methodology was used to analyze survival data, and median times to survival were calculated. A log-rank test at an $\alpha = .05$ level of significance was employed to statistically evaluate differences between survival curves. Additionally, survival analyses were performed for each bipolar subtype.

The percentage of patients stable without relapse for 6 months was analyzed using the Cochran-Mantel-Haenszel chi-square test. Clinical efficacy scales (CGI-S, GAS) were evaluated using analysis of variance (ANOVA) at an $\alpha = 0.05$ level of significance using both observed and last-observation-carried-forward (LOCF) data. Data were also collected at each timepoint before first treatment for a mood episode for life-charting analyses; these data will be presented in a future publication.

Safety. For each study phase, the safety population comprised all patients who received at least one dose of study drug. Safety was assessed by summarizing treatment-emergent adverse experiences and determining changes from screen in clinical laboratory test results, vital signs, and weight values.

Table 1. Patient Disposition

Event	Preliminary Phase (open-label) Lamotrigine N = 324		Randomized Phase (double-blind) N = 182			
			Placebo		Lamotrigine	
	N	%	N	%	N	%
Randomized	N/A		89		93	
Completed	182[a]	56	23	26[b]	37	41[b]
Required additional pharmacotherapy	N/A		49	56[b]	45	50[b]
Withdrawn	142	44	17	19	11	12
Adverse events	35	11	2	2	1	1
Consent withdrawn	26	8	8	9	2	2
Lost to follow-up	19	6	4	5	6	7
Protocol violation	20	6	1	1	2	2
Other	42	13	2	2	0	0

[a]Number of patients eligible for enrollment into randomized phase.
[b]Based on 177 patients included in efficacy analysis: placebo N = 87, lamotrigine N = 90.

Table 2. Patient Characteristics[a]

Characteristics	Preliminary Phase (open-label) Lamotrigine (N = 324)	Randomized Phase (double-blind) Placebo (N = 88)	Randomized Phase (double-blind) Lamotrigine (N = 92)
Women, N (%)	190 (59)	52 (59)	51 (55)
Age, y, mean (range)	38.6 (18–74)	37.4 (18–64)	38.5 (20–61)
Age at onset of affective symptoms, y, mean (range)			
First depressive episode	17.5 (3–45)	17.0 (5–44)	17.3 (3–44)
First manic episode	20.2 (3–54)	19.1 (5–46)	20.7 (3–44)
DSM-IV diagnosis, N (%)			
Bipolar I	225 (69)	60 (68)	68 (74)
Bipolar II	98 (30)	28 (32)	24 (26)
Receiving thyroid supplements for hypothyroidism, N (%)	23 (7)	N/A	N/A
No. of mood episodes, mean (range)			
Last 12 mo	6.3 (2–28)	5.9 (4–14)	6.3 (4–28)
Past 3 y	22.2 (4–160)	23.1 (6–103)	23.9 (5–160)
Prior hospitalizations for a mood episode, mean (range)	1.8 (0–60)	1.3 (0–18)	1.5 (0–15)
Prior suicide attempt, N (%)	117 (36)	34 (39)	25 (27)
Lifetime prevalence of psychosis, N (%)	88 (27)	21 (24)	25 (27)
Mood episode at screening, N (%)	266 (82)	73 (83)	73 (79)
Type of mood episode at screening, N (%)			
Depression	184 (57)	49 (56)	51 (55)
Mania/hypomania	66 (20)	17 (19)	18 (20)
No episode	58 (18)	15 (17)	19 (21)
Mixed	16 (5)	8 (9)	4 (4)
Duration of baseline episode, d, mean (range)	38.2 (1–120)	40.1 (3–120)	40.8 (1–120)
Baseline psychiatric scale scores, mean (SD)			
HAM-D	14.2 (6.9)	6.1 (4.0)	5.4 (3.5)
MRS	7.9 (7.5)	2.9 (2.9)	2.6 (2.9)
CGI-S	3.8 (0.8)	2.1 (0.8)	2.1 (0.8)
GAS	58.0 (11.3)	78.0 (11.0)	77.0 (9.7)

[a]Abbreviations: CGI-S = Clinical Global Impressions-Severity scale, GAS = Global Assessment Scale, HAM-D = 17-item Hamilton Rating Scale for Depression, MRS = Mania Rating Scale.

RESULTS

Sample Composition

Three hundred twenty-four (324) patients received treatment in the preliminary phase of the study at 24 U.S. (N = 292) and 3 Canadian sites (N = 32). Of these patients, 142 did not complete the preliminary phase (the most common reasons were other, N = 42; adverse events, N = 35; and consent withdrawn, N = 26). The remaining 182 patients (ITT population) were randomly assigned to treatment with placebo (N = 89) or lamotrigine (N = 93) during the randomized phase. Sixty patients completed the randomized phase (placebo N = 23, lamotrigine N = 37) clinically stable on monotherapy without evidence of relapse. Ninety-four patients reached study endpoint requiring treatment intervention (placebo N = 49; lamotrigine N = 45) and 28 patients withdrew prematurely prior to study endpoint (placebo N = 17; lamotrigine N = 11) (Table 1).

All 324 patients who entered the preliminary phase were included in the safety analysis. In the randomized phase, 180 patients (placebo N = 88; lamotrigine N = 92) were evaluated for safety. The efficacy analyses included 177 patients (placebo N = 87; lamotrigine N = 90) in the randomized phase. Two patients were withdrawn following enrollment in the randomized phase and were not included in the efficacy or safety analyses; neither patient received study drug before withdrawal. An additional 3 patients were lost to follow-up and had no endpoint efficacy data available for efficacy analysis.

Patient Characteristics

Preliminary phase. Of patients entering the preliminary phase, 59% were women, 69% had bipolar I disorder, and 7% were receiving thyroid supplements for diagnosed hypothyroidism (Table 2). At study entry, the majority of patients were experiencing a mood episode of more than 1 month in duration. The most common mood episode at entry was depression (57%). Lifetime prevalence of psychosis was 27%, and the percentage of patients with prior suicide attempts was 36%.

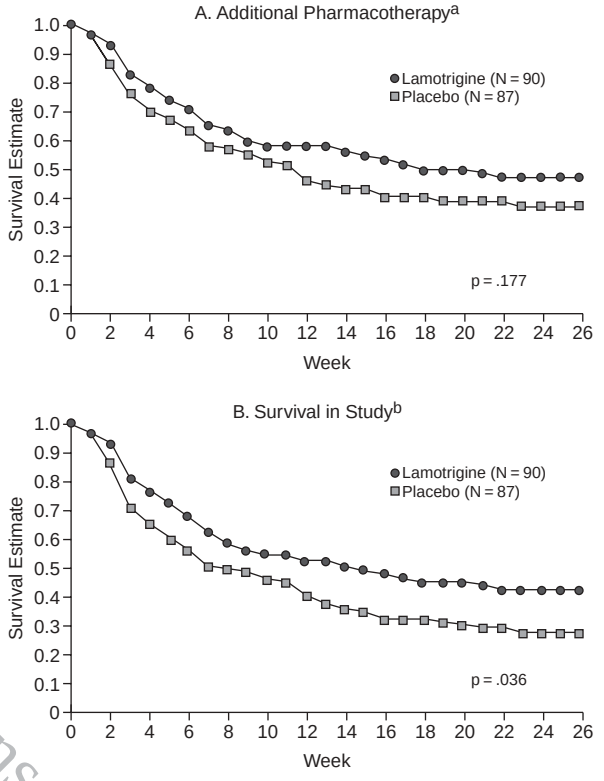
Prior lifetime psychotropics included lithium (68%), carbamazepine (27%), divalproex (57%), lamotrigine (< 1%), antidepressants (82%), and antipsychotics (27%). Concomitant psychiatric medications at study entry included lithium (19%), divalproex (19%), carbamazepine (4%), antidepressants (30%), and antipsychotics (7%). Thirty-nine percent of patients were receiving no psychiatric medications at entry (Table 3). The mean ± SD daily lamotrigine dose during the preliminary phase was 108.5 ± 52.3 (range, 0–400 mg/day).

Randomized phase. Treatment groups were similar with respect to age, sex, race, height, weight, medical history, psychiatric history, prior treatments, response to treatments, and current psychiatric state (see Tables 2 and 3).

Table 3. Treatment History of Psychiatric Medication

	Preliminary Phase (open-label) Lamotrigine (N = 324)		Randomized Phase (double-blind) Placebo (N = 89)		Lamotrigine (N = 93)	
Treatment History	N	%	N	%	N	%
Patients who received ≥ 1 prior treatment for bipolar disorder	283	87	79	89	77	83
Prior lifetime treatment history						
Lithium	192	68	49	62	48	62
Divalproex	162	57	39	49	43	56
Carbamazepine	75	27	11	14	25	33
Antidepressants	232	82	60	76	61	79
Antipsychotics	77	27	16	20	21	27
Concomitant psychiatric medications			N/A		N/A	
Mood stabilizers/anticonvulsants						
Lithium	60	19				
Divalproex	63	19				
Carbamazepine	14	4				
Antidepressants	96	30				
Antipsychotics	24	7				
Benzodiazepines	88	27				
No. of psychiatric medications at baseline						
0	127	39	40	45	45	48
1	86	27	24	27	25	27
2	61	19	15	17	14	15
3	38	12	8	9	7	8
≥ 4	12	4	2	2	2	2

Figure 1. Survival Curves Indicating Length of Study Participation for the Overall Study Population of Patients Treated With Lamotrigine Compared With Patients Treated With Placebo



[a]Patients who withdrew when they required additional pharmacotherapy for emerging mood symptoms.
[b]Patients who prematurely withdrew from the study for any reason (including additional pharmacotherapy for emerging mood symptoms).

Fifty-five percent to 56% of patients were experiencing a depression at study entry (see Table 2). The majority of patients in this study phase were classified as DSM-IV bipolar I (71%). Stratified randomization ensured that the assignment of bipolar I and II patients to the treatment groups was balanced. A comparison of bipolar I and II patients showed no differences with respect to age, sex, race, height, or weight. However, compared with bipolar II patients, bipolar I patients had a greater incidence of past psychotic episodes (33% vs. 13%), suicide attempts (40% vs. 28%), and mean number of lifetime hospitalizations (2.3 vs. 0.7). In the randomized phase, the mean ± SD daily lamotrigine dose was 287.9 ± 94.1 (range, 100–506 mg/day).

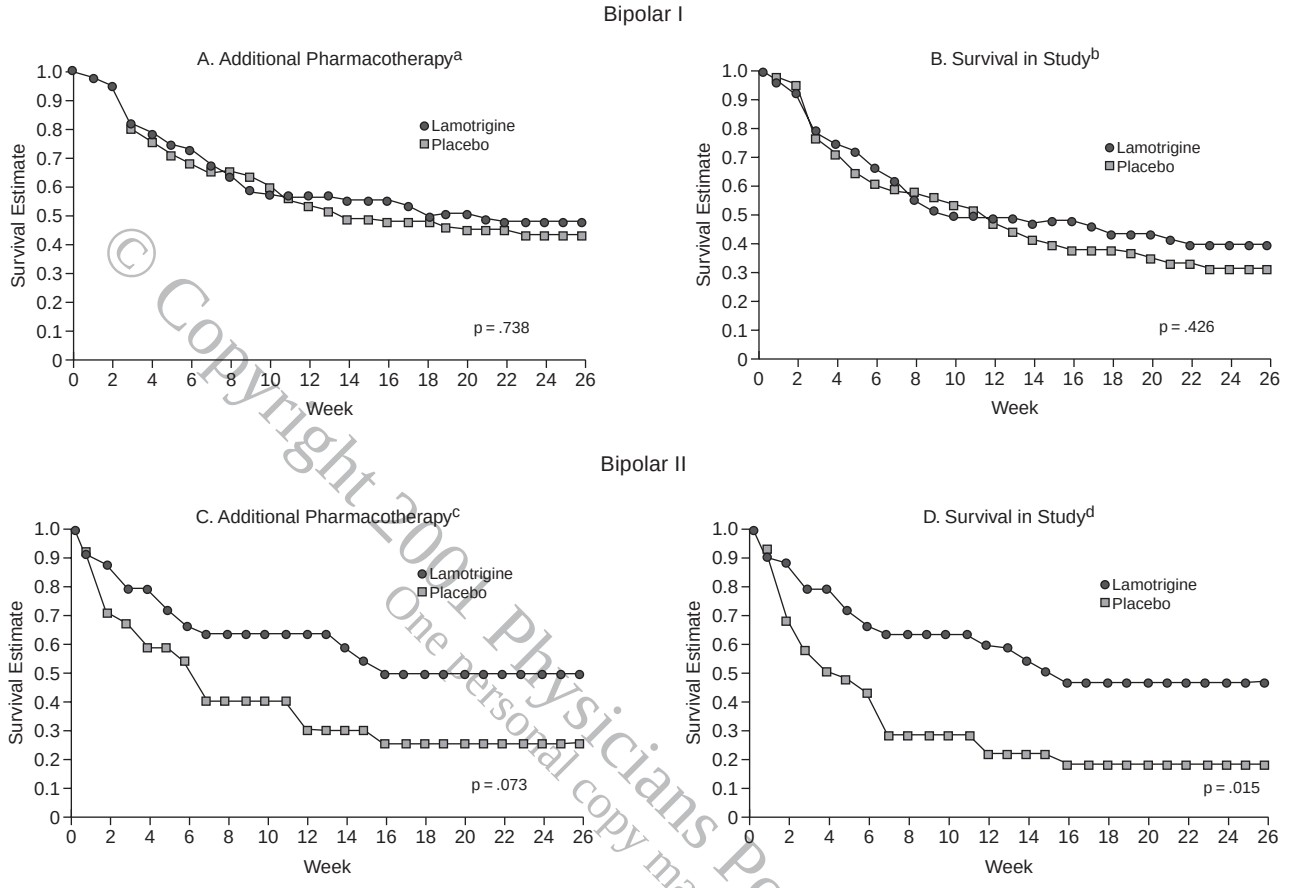
Efficacy

Survival analyses. Forty-nine placebo patients (56%) and 45 lamotrigine patients (50%) required additional pharmacotherapy for emerging symptoms of a mood episode. The difference between the treatment groups in time to additional pharmacotherapy did not achieve statistical significance in the overall efficacy population (p = .177; Figure 1A). The median survival times were 18 weeks for lamotrigine and 12 weeks for placebo. When survival in study was evaluated (any premature discontinuation, including those for additional pharmacotherapy), the difference between the treatment groups was significant (p = .036; Figure 1B). For survival in study, the median survival times were 14 weeks for lamotrigine and 8 weeks for placebo.

Survival analyses were also performed for each bipolar subtype (Figure 2). In the bipolar I subtype (N = 125), no significant treatment differences were observed (Figure 2A and B). In the bipolar II subtype (N = 52), there was a trend toward a statistically significant difference between treatment groups for time to additional pharmacotherapy (p = .073) and a significant difference for survival in study (p = .015) (Figure 2C and D). Median survival time without additional pharmacotherapy for the bipolar II subtype was 17 weeks for lamotrigine and 7 weeks for placebo.

The majority of patients (80%) requiring additional pharmacotherapy were treated for depressive symptoms; 20% were treated for emerging manic, hypomanic, or mixed symptoms. The proportion of patients needing intervention for depressive versus manic/hypomanic/mixed symptoms did not differ between treatment groups. At time of additional pharmacotherapy, the mean ± SD HAM-D scores for those patients receiving treatment for depression were 19.5 ± 6.1 for lamotrigine and 17.9 ± 5.7 for placebo;

Figure 2. Survival Curves Indicating Length of Study Participation for Bipolar I (N = 125) and II (N = 52) Subtypes Treated With Lamotrigine Compared With Placebo



[a]Bipolar I patients who withdrew when they required additional pharmacotherapy for emerging mood symptoms.
[b]Bipolar I patients who prematurely withdrew from the study for any reason (including additional pharmacotherapy for emerging mood symptoms).
[c]Bipolar II patients who withdrew when they required additional pharmacotherapy for emerging mood symptoms.
[d]Bipolar II patients who prematurely withdrew from the study for any reason (including additional pharmacotherapy for emerging mood symptoms).

the mean ± SD MRS scores for this subgroup were 5.2 ± 5.2 for lamotrigine and 5.6 ± 6.1 for placebo. The mean ± SD MRS scores for those patients receiving treatment for mania/hypomania/mixed symptoms were 18.0 ± 8.9 for lamotrigine and 14.4 ± 9.0 for placebo; the mean ± SD HAM-D scores for this subgroup were 13.8 ± 6.7 for lamotrigine and 14.3 ± 4.9 for placebo.

Stable without relapse for 6 months. The percentage of patients who completed the 6-month randomized phase clinically stable on monotherapy without evidence of relapse was significantly greater in the lamotrigine group than in the placebo group. Of the 60 patients who were stable for 6 months of monotherapy, 37 were in the lamotrigine group, comprising 41% (37/90) of that group, compared with 23 in the placebo group (p = .03), comprising 26% (23/87) of the placebo group. The difference for lamotrigine versus placebo was not statistically significant for the bipolar I subtype, but was significant (46% vs. 18%, respectively; p = .04) for the bipolar II subtype (Figure 3).

Additional efficacy measures. In the randomized phase, CGI-S and GAS scores were used to provide additional measures of clinical stability (data not shown). For the overall study population and the bipolar I subtype, no statistically significant differences were found between treatment groups on CGI-S change from baseline scores using LOCF. For the bipolar II subtype, trends toward statistically significant differences (p < .10) favoring the lamotrigine group were observed in CGI-S scores compared with the placebo group at weeks 6 and 12. No statistically significant differences favoring lamotrigine were observed between groups in GAS change from baseline scores in the general cohort of patients (LOCF). Significant differences favoring lamotrigine were noted at weeks 3 (p = .03), 6 (p = .02), and 12 (p = .03) in the bipolar II subtype; however, no significant differences were noted at any timepoint for the bipolar I subtype. There were no significant differences observed in the change from baseline LOCF analyses at any timepoint for the 17-item HAM-D or the MRS.

Figure 3. Percentage of Patients Stable Without Relapse for 6 Months on Lamotrigine Treatment or Placebo

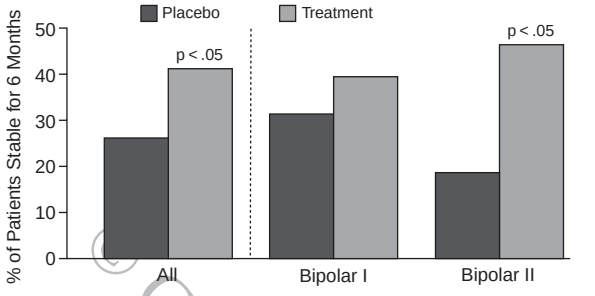


Table 4. Common (≥ 10%) Treatment-Emergent Adverse Events

	Preliminary Phase (open-label) Lamotrigine N = 324		Randomized Phase (double-blind) Placebo N = 88		Lamotrigine N = 92	
Event	N	%	N	%	N	%
Headache	114	35	15	17	21	23
Nausea	50	15	10	11	13	14
Infection	42	13	10	11	11	12
Rash	44	14	2	2	3	3
Dizziness	37	11	3	3	8	9
Influenza	32	10	8	9	6	7
Dream abnormality	31	10	1	1	2	2
Pain	28	9	7	8	9	10
Accidental injury	17	5	4	5	10	11

Safety

A total of 265 patients (82%) reported treatment-emergent adverse events during the preliminary phase (Table 4). The most common adverse events (≥ 10%) were headache, infection, influenza, nausea, dream abnormality, dizziness, and rash. In the randomized phase, 122 patients (67% lamotrigine; 68% placebo) experienced adverse events in each treatment group (see Table 4). During the randomized phase, the most common adverse events were headache, nausea, infection, pain, and accidental injury.

During the randomized phase, adverse events considered reasonably related to study drug did not differ significantly (lamotrigine N = 28, 30%; placebo N = 24, 27%), and the majority were mild (lamotrigine N = 16, placebo N = 11) or moderate (lamotrigine N = 10, placebo N = 10) in intensity. The most common of these adverse events included nausea (lamotrigine N = 4, 4%; placebo N = 4, 5%) and headache (lamotrigine N = 6, 7%; placebo N = 8, 9%).

Treatment-related rash occurred in 25 preliminary-phase patients (8%). No patients in the randomized phase had treatment-related rash. No incidences of serious rash occurred during the study.

Adverse events led to withdrawal in 36 preliminary-phase patients (11%) and 4 randomized-phase patients (lamotrigine N = 2, 2%; placebo N = 2, 2%). The most common adverse event in the preliminary phase that led to withdrawal was rash; 15 patients (5%) with rash withdrew from the study (the protocol required withdrawal of patients with rash of unknown etiology).

In the preliminary phase, 16 patients experienced serious adverse events. Four of these patients were hospitalized for mood-related events prior to starting open-label lamotrigine and were withdrawn from the study. Twelve patients experienced treatment-emergent serious adverse events. Eight patients required psychiatric hospitalization: 4 patients for mania/exacerbation of mania (1 was considered reasonably attributable to study treatment), 3 for depression/suicidal/suicide attempt, and 1 patient for delusions (considered reasonably attributable to study treatment). Of the remaining events, only cerebellar syndrome was considered potentially treatment related.

In the randomized phase, 3 patients experienced serious adverse events; none were considered reasonably attributable to study treatment. One patient in the placebo group had a basal cell carcinoma; another placebo patient had a benign skull tumor. One patient in the lamotrigine group, who had a previously diagnosed history of mitral valve prolapse, experienced a constellation of symptoms (dehydration, faintness, migraine, shortness of breath) associated with an episode of tachycardia. No serious psychiatric events occurred during this phase. No serious rash was reported in either phase.

The mean change in body weight from screen to day 1 of randomization or premature withdrawal (N = 227) was 0.3 kg. From screen to end of the study, mean weight for the lamotrigine monotherapy completers (N = 35) remained unchanged. During the randomized phase, the placebo monotherapy completers (N = 35) had a mean weight change of –0.3 kg, and the lamotrigine monotherapy completers had a mean weight change of 1.1 kg. No significant changes in physical examination, hematology, or clinical laboratory parameters were reported during the study.

DISCUSSION

This lamotrigine monotherapy study is the first double-blind, placebo-controlled, long-term maintenance evaluation of a large population of prospectively defined patients with rapid-cycling bipolar disorder. The observed differences in median survival times favoring lamotrigine in the primary outcome of time to additional pharmacotherapy did not reach statistical significance. When overall survival in study (including all premature discontinuations) was evaluated, the differences significantly favored lamotrigine. In both analyses, the survival time was 6 weeks longer for lamotrigine than placebo. The percentage of patients who remained clinically stable for 6 months on monotherapy was significantly greater in the lamotrigine group than in placebo.

Bipolar disorder is a disorder of impulse control and impaired judgment, and poor compliance is a frequent consequence of both. We therefore hypothesized that premature treatment discontinuations are related to early signs of relapse. Thus, one clinically relevant measure of efficacy is survival in the study to the point of withdrawal for any reason. The primary efficacy measure, time from randomization to additional pharmacotherapy, and the overall efficacy measure, time from randomization to withdrawal for any reason, served as naturalistic and ethical safeguards for patients who began to relapse during the study.

The majority of patients requiring additional pharmacotherapy were treated for depressive symptoms, indicating that the frequent recurrence of depression may be the hallmark of most rapid-cycling patients. This would suggest that, at the time of presentation and treatment, a prominent feature of a rapid-cycling pattern is treatment-refractory depression. To our knowledge, other published studies of patients with rapid cycling have not provided evidence to clarify this issue. Information needed includes the frequency of depressive episodes and the cumulative time spent in depression relative to hypomania/mania in rapid-cycling patients. Further analyses are underway to evaluate this issue.

Differences favoring lamotrigine were consistently greater for bipolar II than bipolar I patients. This was unexpected since lamotrigine has previously been shown to possess efficacy in the acute treatment of bipolar I depression.[14] In the analysis involving patients stable without relapse for 6 months, the lamotrigine arm appeared to exhibit similar degrees of prevention in both bipolar subtypes. For example, the apparent differential effect of lamotrigine over placebo in the percentage of bipolar II patients experiencing clinical stability without relapse (46% vs. 18%), compared with that in bipolar I patients (39% vs. 31%), appears to have been due to differences in the performance of placebo. These differences will be the topic of a future article. While it remains unclear what accounts for different response rates in the bipolar subtypes, these findings support the subtyping topology adopted in the DSM-IV.

Several novel design elements were employed in the current study. The first phase of this study employed an "enriched" discontinuation design in which patients who met stabilization criteria were randomly assigned to the 2 treatment groups in the maintenance phase. This design has been the most commonly used method to evaluate the maintenance efficacy of lithium in bipolar disorder and is considered "enriched" because it randomizes a homogeneous cohort of patients who have demonstrated good compliance and a marked response to an experimental medication. As a result, there is less variance in the cohort of patients randomly assigned to maintenance therapy.[31] Rapid cycling was prospectively defined, and a large number of patients were enrolled. The preliminary phase of this study followed the routine clinical practice of introducing a new medication while ineffective medications were gradually discontinued. Since concomitant psychiatric medications, including lithium, were tapered in the preliminary phase, usually over a 4- to 8-week period, discontinuation-induced relapse from rapid discontinuation of lithium and other psychiatric medications is unlikely to have confounded the randomized data.

This study had several limitations. Because of the absence of monotherapy data relevant to this design, no statistical justification was used in determining sample size. It was retrospectively determined that approximately 200 patients per treatment arm would have been required to provide 80% power to identify the observed 6-week difference in time to additional pharmacotherapy as statistically significant. The actual enrollment of less than 100 patients per treatment arm limited the power of the primary outcome analysis to approximately 47%. In contrast, the analysis of survival in study was retrospectively determined to have been powered at approximately 83%. At the time of randomization, patients assigned to placebo had open-label lamotrigine abruptly discontinued. Although rebound relapse into a mood episode after the abrupt discontinuation of lamotrigine has been reported in neither the neurologic nor psychiatric literature, this methodological feature remains a possible confound. The design of this study did not permit an analysis of time to relapse into a full episode of depression, hypomania, or mania since patients were withdrawn at the first signs of relapse. In addition, this study enrolled a higher proportion of patients with bipolar I disorder than is thought to occur in the rapid-cycling population. The reason for this sample distribution is unclear and adds to the controversy regarding the actual incidence of bipolar I and II in rapid-cycling bipolar disorder. These results may have also been influenced by what may have been a high placebo-response rate in patients with bipolar I disorder, a finding also seen in another recent bipolar maintenance study.[32] Interestingly, the response to treatment with placebo was higher in bipolar I patients than in bipolar II patients. This may account for the lack of statistical significance in several bipolar I analyses. The reasons for this apparently high placebo-response rate within the bipolar I group are unclear; however, it is possible that a selection bias on the part of investigators may have also minimized the enrollment of more severely ill patients. Given the striking differences between the bipolar I and II patients, and prior data supporting the use of lamotrigine in bipolar I depression,[14] it is quite likely that additional factors may have led to the apparent high placebo-response rate in some patients with bipolar I disorder.

Lamotrigine was well tolerated during the current study. The type and frequency of adverse events after lamotrigine treatment were comparable to placebo. Most

adverse events were mild or moderate in intensity, and no significant weight gain was reported. Serious adverse events related to lamotrigine were rare. There were no incidents of serious rash or hypersensitivity syndrome associated with lamotrigine treatment. Overall, these long-term safety data are consistent with and augment recent placebo-controlled short-term data in bipolar disorder.[14]

Mood stabilizers, the foundation of treatment for bipolar disorder, have been defined as medications that possess efficacy in one phase of the illness without causing a negative effect on other phases of the illness (i.e., without causing switching)[33] or medications that have efficacy in both phases of the illness.[31] In previous studies, lamotrigine has shown efficacy in bipolar depression without causing switching to hypomania/mania.[14–22] Efficacy in mania has not been established. In this study, lamotrigine demonstrated efficacy in the prevention of the recurrence of mood symptoms over a 6-month period. On the basis of at least one of the published definitions of a mood stabilizer,[33] the available data suggest that lamotrigine monotherapy possesses both antidepressant and mood-stabilizing properties, the latter supported by the improved survival in study patients with bipolar II disorder.

The results of this study suggest that lamotrigine may be a well-tolerated and effective mood stabilizer with prophylactic properties when used as monotherapy in some patients with rapid-cycling bipolar disorder. Lamotrigine may be an especially effective mood stabilizer for patients diagnosed with bipolar II disorder. It is noteworthy that most patients who entered the study and were subsequently randomly assigned to double-blind treatment were in a depressive episode, which further supports the antidepressant properties of lamotrigine reported in other studies.[14,15] The positive results of this study add to a considerable number of open-label lamotrigine studies[15–19] and 2 other placebo-controlled studies[14,22] in bipolar disorder and rapid-cycling bipolar disorder. Additional studies are underway to further elucidate the efficacy of lamotrigine in patients with rapid-cycling bipolar disorder and other treatment-refractory variants of the illness.

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

Financial disclosure: Dr. Calabrese is a consultant for and has received grant/research support and honoraria from Glaxo Wellcome. Dr. Suppes is a consultant for, has received grant/research support and honoraria from, and/or is a member of the speakers or advisory board for Glaxo Wellcome, Eli Lilly, Novartis, Janssen, AstraZeneca, Bristol-Myers Squibb, Abbott, Pfizer, Pharmaceutical Research Institute, the Stanley Foundation, the Lattner Foundation, and Timberlawn. Dr. Bowden is a consultant for Abbott Laboratories, Glaxo Wellcome, Janssen, Lilly Research, Sanofi Synthelabo, and UCB Pharma, Inc.; has received grant/research support from Abbott Laboratories, Bristol-Myers Squibb, Glaxo Wellcome, Janssen, Lilly Research, National Institute of Mental Health, Parke-Davis, R W. Johnson Pharmaceutical Institute, SmithKline Beecham, and the Stanley Foundation; and is a member of the speakers board for Abbott Laboratories, AstraZeneca, Glaxo Wellcome, Janssen, Lilly Research, and Pfizer. Dr. Sachs is a consultant for Abbott, Glaxo Wellcome, Lilly, Janssen, Sanofi, and Solvay; has received grant/research support from Abbott, Glaxo Wellcome, Lilly, Solvay, and Janssen; has received honoraria from Abbott, Glaxo Wellcome, Lilly, SmithKline Beecham, Bristol-Myers Squibb, Janssen, and Sanofi; and is a member of the speakers or advisory board for Abbott, Glaxo Wellcome, Lilly, SmithKline Beecham, Bristol-Myers Squibb, Janssen, and Sanofi. Dr. Swann is a consultant for Abbott, Glaxo Wellcome, Janssen, Lilly, and Shire Laboratories; has received grant/research support from Abbott, Glaxo Wellcome, Janssen, Bristol-Myers Squibb, Shire Laboratories, and Pharmacia and Upjohn; has received honoraria from Abbott, Parke-Davis, and Janssen; and is a member of the speakers or advisory board for Abbott, Parke-Davis, and Janssen. Dr. McElroy is a consultant for, has received grant/research support and honoraria from, and is a member of the speakers or advisory board for Glaxo Wellcome. Drs. Ascher, Earl, and Greene and Ms. Monaghan are employees of Glaxo Wellcome.

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Acknowledgment: Participants in the Lamictal 614 Study Group

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