A Double-Blind Placebo-Controlled Study of Lamotrigine Monotherapy in Outpatients With Bipolar I Depression

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Background: More treatment options for bipolar depression are needed. Currently available antidepressants may increase the risk of mania and rapid cycling, and mood stabilizers appear to be less effective in treating depression than mania. Preliminary data suggest that lamotrigine, an established antiepileptic drug, may be effective for both the depression and mania associated with bipolar disorder. This is the first controlled multicenter study evaluating lamotrigine monotherapy in the treatment of bipolar I depression.

Method: Outpatients with bipolar I disorder experiencing a major depressive episode (DSM-IV, N = 195) received lamotrigine (50 or 200 mg/day) or placebo as monotherapy for 7 weeks. Psychiatric evaluations, including the Hamilton Rating Scale for Depression (HAM-D), the Montgomery-Asberg Depression Rating Scale (MADRS), Mania Rating Scale, and the Clinical Global Impressions scale for Severity (CGI-S) and Improvement (CGI-I) were completed at each weekly visit.

Results: Lamotrigine 200 mg/day demonstrated significant antidepressant efficacy on the 17-item HAM-D, HAM-D Item 1, MADRS, CGI-S, and CGI-I compared with placebo. Improvements were seen as early as week 3. Lamotrigine 50 mg/day also demonstrated efficacy compared with placebo on several measures. The proportions of patients exhibiting a response on CGI-I were 51%, 41%, and 26% for lamotrigine 200 mg/day, lamotrigine 50 mg/day, and placebo groups, respectively. Adverse events and other safety results were similar across treatment groups, except for a higher rate of headache in the lamotrigine groups.

Conclusion: Lamotrigine monotherapy is an effective and well-tolerated treatment for bipolar depression.

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A complete list of the members of the Lamictal Study 602 Group is given at the end of this article.

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More effective treatments for the depressive episodes of bipolar disorder are needed. Currently available mood stabilizers, including lithium, are effective in the treatment of mania but appear to be less effective in the treatment of bipolar depression.[1] The adjunctive use of antidepressant medications is common, but this practice can put patients with bipolar disorder at increased risk for the development of hypomania, mania, or cycle acceleration.[2] During the development of the antiepileptic compound lamotrigine, the drug was observed to improve mood, alertness, and social interactions in some patients.[3] These early observations in patients with epilepsy stimulated interest in the evaluation of lamotrigine as an antidepressant and mood stabilizer. Open-label clinical reports involving over 200 patients suggest that lamotrigine may possess a broad spectrum of mood stabilizing efficacy in bipolar I and II disorder when given as adjunct treatment or as monotherapy.[4–18]

A series of controlled studies has been initiated to evaluate the efficacy and safety of lamotrigine in the various phases of bipolar I and II disorder. This report presents data from the first study in this series, which compared 2 doses of lamotrigine with placebo in the treatment

of a major depressive episode in patients with bipolar I disorder.

METHOD

Patients

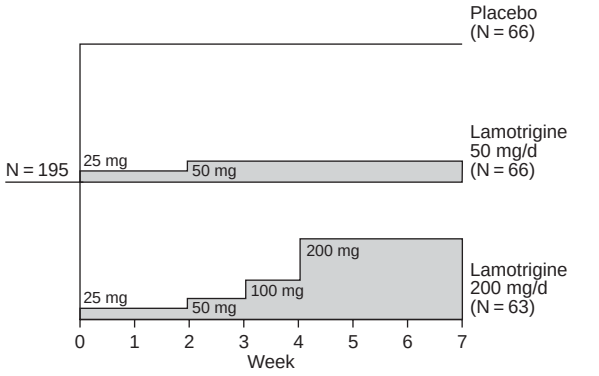
Men and women at least 18 years of age were eligible for the study if they were diagnosed with bipolar I disorder, as defined by DSM-IV criteria, and had at least 2 previous mood episodes during the past 10 years, at least 1 of which was a manic or mixed episode. The diagnosis was confirmed by the Structural Clinical Interview for DSM-IV. Eligible patients were currently experiencing a major depressive episode with a duration ≥ 2 weeks but ≤ 12 months. A minimum score of 18 on the 17-item Hamilton Rating Scale for Depression (HAM-D)[19,20] was required at study entry. Patients with rapid-cycling bipolar disorder; abnormal thyroid function tests; a diagnosis of or treatment for panic disorder, obsessive-compulsive disorder, social phobia, or bulimia nervosa in the previous 12 months; a history of substance dependence (previous year) or abuse (previous month) or with a positive toxicological screen; a chronic cardiac, renal, or hepatic condition or an unstable medical condition; or epilepsy were excluded. Pregnant or lactating women and patients who were actively suicidal were also excluded. Patients with worsening of psychiatric status such that symptoms constituted a danger to them or to others were to be discontinued. Patients must have discontinued any psychoactive drug within a time equal to 5 elimination half-lives prior to randomization.

Study Design and Procedures

This randomized, double-blind, parallel-group, multicenter study (Glaxo Wellcome Protocol 105-602) was conducted to compare the efficacy and safety of lamotrigine monotherapy and placebo in the treatment of bipolar I depression. Careful consideration was given to the use of placebo in this trial. Institutional review board (United States) and ethics committee (outside the United States) approvals were obtained, and patients provided written, informed consent. After screening and baseline assessments confirmed that entry criteria were met, equivalent numbers of patients were randomly assigned to treatment with a target dose of either lamotrigine 50 mg/day (25 mg b.i.d., N = 66), lamotrigine 200 mg/day (100 mg b.i.d., N = 63), or placebo tablets (b.i.d., N = 66) (Figure 1). To balance the effects of recent use of lithium, randomization was stratified according to intensity of treatment with lithium (presence or absence of plasma levels of ≥ 0.4 mmol/L or dosing of ≥ 600 mg/day for ≥ 1 month) during the 5 months preceding study entry.

Patients randomly assigned to lamotrigine 50 or lamotrigine 200 mg/day received active lamotrigine as 25-mg chewable, dispersible tablets. The lamotrigine dose was

Figure 1. Flow Diagram of Study Design and Dose Escalation Schedule



escalated according to the following schedule to reach a target of 50 mg/day (weeks 1–2, 25 mg q.d.; weeks 3–7, 25 mg b.i.d.) or 200 mg/day (weeks 1–2, 25 mg q.d.; week 3, 25 mg b.i.d.; week 4, 50 mg b.i.d.; weeks 5–7, 100 mg b.i.d.) as shown in Figure 1. Placebo tablets were identical in appearance to the active drug. The number of placebo tablets was adjusted at each week and for each lamotrigine dose so that the total number of tablets administered per day (lamotrigine plus placebo) was always 8. Patients were provided with blister cards containing each week's medication. Compliance with the prescribed dosing regimen was determined by returned tablet counts at each treatment visit. The only other psychoactive drugs permitted were chloral hydrate, lorazepam, temazepam, or oxazepam as needed for control of agitation, insomnia, and hostile behaviors during the first 3 weeks of the treatment phase.

Clinic visits were conducted at screening (within 14 days prior to treatment), baseline (the day prior to the start of treatment), on the fourth day of treatment, and the end of every week for the 7-week duration of treatment. At the screening visit, patients underwent the following assessments: demographic characteristics, a modified version of the Structured Clinical Interview for DSM-IV (SCID),[21] psychiatric history (including age at onset of affective symptoms), physical examination, skin rash history, clinical laboratory tests (including thyroid function tests), urinalysis, urine screen for illicit drugs, electrocardiogram, and psychiatric rating scales including the HAM-D, the Montgomery-Asberg Depression Rating Scale (MADRS),[22] the Mania Rating Scale (first 11 items from the Schedule for Affective Disorders and Schizophrenia, Change Version; MRS),[23] and the Clinical Global Impressions scale for Severity (CGI-S).[24] At the baseline visit and each treatment visit, the following assessments were completed: HAM-D, MADRS, MRS, CGI-S, and Clinical Global Impressions scale for Improvement (CGI-I, day 4 onward)[24]; adverse event assessment by standardized verbal probe; and record of study and other

Table 1. Patient Disposition

Event	Placebo N	Placebo %	Lamotrigine 50 mg/day N	Lamotrigine 50 mg/day %	Lamotrigine 200 mg/day N	Lamotrigine 200 mg/day %
Randomized	66		66		63	
Withdrawn prematurely	19	29	23	35	18	29
Adverse event	10	15	12	18	10	16
Death	1	2	0	0	0	0
Inadequate response	2	3	0	0	1	2
Protocol violation	1	2	1	2	2	3
Other	5	8	10	15	5	8
Completed	47	71	43	65	45	71
Received ≥ 1 dose of study drug (safety population)	65		66		63	
Had baseline and ≥ 1 post-randomization assessment (efficacy population)	65		64		63	

medications. The investigators' reports of clinically significant manifestations of manic, hypomanic, or mixed episodes were recorded as adverse events whether or not they met full DSM-IV criteria. Patients who developed a rash were withdrawn unless the rash was clearly unrelated to use of the study drug. At the last treatment visit (day 50 or discontinuation), patients were given physical examinations and clinical laboratory tests.

Blood samples for determination of trough lamotrigine plasma concentrations were drawn at screening, 2 and 4 weeks after the start of treatment, and at the last treatment visit (day 50 or discontinuation). The potential correlation between plasma concentrations and response will be the subject of a future report.

Patients who completed this 7-week study could elect to enter a 1-year open-label continuation study. Patients who withdrew prematurely or chose not to enter the continuation study discontinued lamotrigine dosing without taper. They returned 2 weeks after study treatment for a follow-up visit with psychiatric assessments and reporting of adverse events and concomitant medications. Patients who elected to participate in the continuation trial were initiated (placebo patients) or continued (lamotrigine patients) on lamotrigine treatment during a blinded transition period.

Data Analysis

Efficacy. The study was powered to detect a 5.0-point difference between lamotrigine and placebo on 17-item HAM-D change from baseline scores, estimating mean ± SD placebo change from baseline scores of 6.0 ± 7.0, a 2-sided alpha level of .05, and a power of 0.90. Based on these assumptions, approximately 60 patients were enrolled to provide 40 completed patients per treatment group. All patients who completed baseline assessments and at least 1 postrandomization efficacy assessment were included in the efficacy analyses. In addition to analysis of observed data at each time point, efficacy variables were assessed using last-observation-carried-forward (LOCF) scores. CGI-I scores and change from baseline scores for the other overall efficacy scales (17-item HAM-D, 31-item HAM-D, HAM-D item 1, MADRS, MRS, and CGI-S) were tested for treatment group differences at each week using analysis of variance (ANOVA). Significant differences in change scores were determined for each visit using a 2-tailed comparison alpha level of .05. In addition, a responder analysis was performed on the last observed 17-item HAM-D, MADRS, and CGI-I scores comparing the rate of response among treatment groups by a stratum-adjusted Cochran-Mantel-Haenszel chi-square analysis. A response was categorically defined as 50% or more reduction on the 17-item HAM-D or MADRS scales or a rating of very much improved or much improved on the CGI-I scale.

Medication compliance. All patients who received at least 1 dose of study medication and had dosing records were included in the compliance analyses. Medication compliance during the 50-day treatment phase was assessed from compliance records (tablets taken/tablets prescribed), and the percentage of patients with greater than 70% compliance was calculated.

Safety. All patients who received at least 1 dose of study drug were included in the safety analysis. The incidence of patients reporting a treatment-emergent adverse event (one emerging or worsening after beginning study drug treatment) was summarized. To compare the incidence of adverse events between treatment groups, 95% confidence intervals were determined. For clinical laboratory tests and vital signs, all patients with clinically significant changes, i.e., values or changes from baseline outside predetermined ranges, were listed.

RESULTS

Sample Composition

One hundred ninety-five patients (66 placebo, 66 lamotrigine 50 mg/day, and 63 lamotrigine 200 mg/day) were randomized to treatment at 15 centers in the United States and 6 centers in the United Kingdom, France, and Australia. Approximately 30% of the patients withdrew prematurely from the trial, most frequently for adverse events or other reasons (e.g., lost to follow-up or withdrawn consent, Table 1). Four patients were withdrawn for protocol violations (noncompliance with scheduled visits in 3 cases and continued use of disallowed psychotropic medications in the other). The rate of withdrawals and completions and the specific reasons for withdrawal were similar across the 3 treatment groups. All patients but one on placebo (who was immediately lost to follow-up and had no record of study drug administration) were included in the safety analyses. The 192 patients who received at least 1 dose of study medication and completed the baseline and at least 1 postrandomization assessment were included in the efficacy analyses.

Table 2. Patient Characteristics[a]

Characteristic	Placebo (N = 66)	Lamotrigine 50 mg/day (N = 66)	Lamotrigine 200 mg/day (N = 63)
Sex, N (%)			
Male	27 (41)	22 (33)	28 (44)
Female	39 (59)	44 (67)	35 (56)
Age, y			
Mean	42	41	42
Range	21–71	19–75	21–66
Age at onset of affective symptoms, y			
Mean	21	22	21
Range	5–50	4–68	6–53
No. mood episodes in last 12 mo per patient, mean ± SD	2.2 ± 0.8	2.2 ± 0.8	2.2 ± 0.9
No. mood episodes in lifetime per patient,[b] mean ± SD	17.4 ± 16.0	17.2 ± 18.1	15.9 ± 16.1
Duration of current episode, N (%)			
2–8 wk	19 (29)	26 (39)	23 (37)
> 8–24 wk	28 (42)	29 (44)	26 (41)
> 24 wk	19 (29)	11 (17)	14 (22)
Intensity of depression,[c] N (%)			
Mild	0 (0)	3 (5)	2 (3)
Moderate	40 (61)	38 (58)	34 (54)
Severe	23 (35)	23 (35)	24 (38)
Severe with psychosis	3 (5)	2 (3)	3 (5)
CGI-S score at baseline, N (%)			
Normal	0 (0)	0 (0)	0 (0)
Borderline mentally ill	0 (0)	0 (0)	0 (0)
Mildly ill	1 (2)	2 (3)	6 (10)
Moderately ill	43 (65)	42 (64)	32 (51)
Markedly ill	15 (28)	15 (23)	19 (30)
Severely ill	7 (11)	7 (11)	6 (10)
Extremely ill	0 (0)	0 (0)	0 (0)
Melancholic features, N (%)	33 (50)	26 (39)	25 (40)
Prior hospitalization for mood episode, N (%)	41 (62)	29 (44)	32 (51)
Prior suicide attempts, N (%)	24 (36)	21 (32)	20 (32)
Lithium use in last 5 mo according to study criteria,[d] N (%)	15 (23)	15 (23)	12 (19)

[a]Abbreviation: CGI-S = Clinical Global Impressions scale for Severity.
[b]Excluding patients with episodes too numerous to count.
[c]Based on Structured Clinical Interview for DSM-IV.
[d]Plasma levels ≥ 0.4 mmol/L or dosing of ≥ 600 mg/day for ≥ 1 month.

Patient Characteristics

The gender, age, psychiatric history, and baseline illness of the patients were similar across treatment groups (Table 2). Approximately 60% of patients in each treatment group were women, and the mean age was approximately 40 years. Over 50% of the patients had been previously hospitalized, and over 30% had attempted suicide. For the majority of patients, the current depressive episode had lasted for at least 8 weeks prior to enrollment. Other indications of their baseline severity (CGI-S, SCID, melancholia) suggest that these patients were moderately to markedly ill when enrolled in the study. Randomization was stratified to balance the groups for the use of lithium at minimally active levels in the 5 months prior to study entry.

Table 3. Previous Treatment for Bipolar Disorder (N = 178)

Treatment	Patients With Prior Treatment[a]	Responders[b] (%)	Intolerant[b] (%)
Antidepressants	85	52	73
Lithium	65	59	34
Valproate	37	45	29
Neuroleptics	28	55	33
Carbamazepine	22	36	44
Electroconvulsive therapy	7	67	25

[a]Percentage based on total number of patients with any prior treatment.
[b]Percentage based on total number of patients with prior treatment in each drug category.

One hundred seventy-eight (91%) of 195 patients had been previously treated for bipolar disorder. Table 3 describes the prior medication history of this patient population, including the percentage responding to and the percentage unable to tolerate individual medications. The incidence of prior treatment described in Table 3 was similar across treatment groups.

Efficacy Results

Observed and LOCF results for all efficacy scales at the last treatment visit are provided in Table 4.

HAM-D scores. 17-Item HAM-D. The mean ± SD baseline 17-item HAM-D score was 24 ± 4 in each treatment group. Both lamotrigine groups demonstrated a mean 13-point improvement in 17-item HAM-D scores over the course of treatment, which was significantly greater than the 9-point improvement in placebo group scores (Table 4; observed scores). Significant improvement for lamotrigine 200 mg/day, but not lamotrigine 50 mg/day, compared with placebo was first noted at week 5 (Figure 2). LOCF results were qualitatively similar, reaching a trend ($p = .084$) at endpoint for the lamotrigine 200-mg/day group only.

HAM-D Item 1. Mean scores for HAM-D item 1 (depressed mood) were reduced over the treatment period by at least 1.1 points in each of the lamotrigine groups versus at least 0.6 points in the placebo group (observed and LOCF scores; see Table 4 and Figure 2). Significant differences compared with placebo were observed by the third week of treatment and continued throughout treatment.

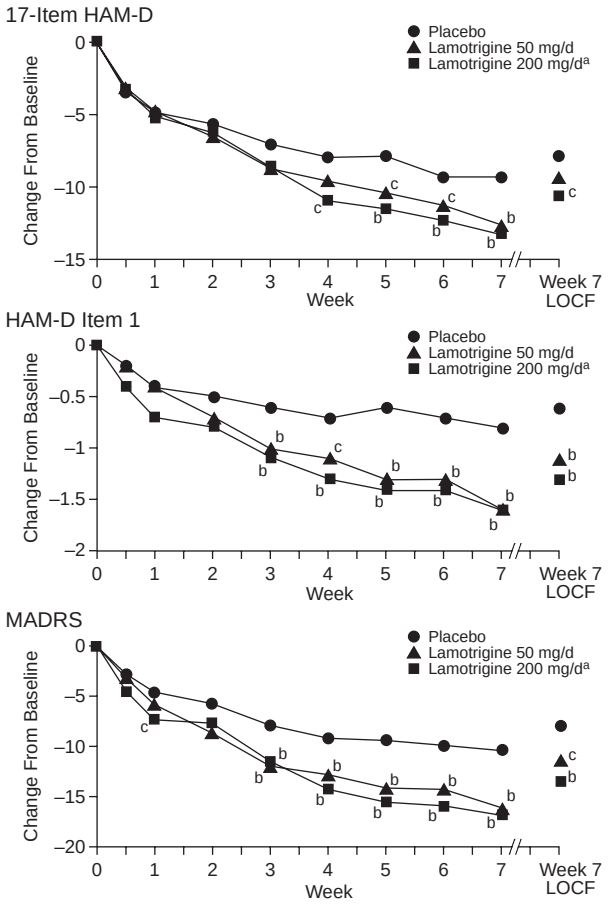
31-Item HAM-D. Mean reductions in 31-item HAM-D of 19.1 in the lamotrigine 50-mg/day and lamotrigine 200-mg/day groups approached significance compared with placebo ($p = .072$ and $p = .086$, respectively, for observed scores; see Table 4). At week 4 only, the mean observed score for the lamotrigine 200-mg/day group was

Table 4. Baseline and Change From Baseline Scores (mean ± SD) on Efficacy Scales at Week 7[a]

	Placebo						Lamotrigine 50 mg/day						Lamotrigine 200 mg/day					
	Baseline Score (N = 65)		Observed Change (N = 47)		LOCF Change (N = 65)		Baseline Score (N = 64)		Observed Change (N = 43)		LOCF Change (N = 64)		Baseline Score (N = 63)		Observed Change (N = 45)		LOCF Change (N = 63)	
Scale	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
17-Item HAM-D	24.3	3.9	–9.3	6.9	–7.8	7.9	23.7	4.4	–12.6[b]	7.7	–9.3	8.9	23.8	3.9	–13.2[b]	7.4	–10.5[c]	8.1
HAM-D item 1	2.8	0.5	–0.8	1.1	–0.6	1.0	2.8	0.6	–1.6[b]	1.1	–1.1[b]	1.3	2.8	0.6	–1.6[b]	1.1	–1.3[b]	1.2
31-Item HAM-D	35.8	5.6	–14.7	11.4	–12.1	12.8	35.1	7.4	–19.1[c]	11.8	–14.2	13.9	34.5	6.8	–19.1[c]	11.2	–15.7	12.2
MADRS	28.9	5.9	–10.2	9.0	–7.8	10.4	28.0	6.5	–16.1[b]	9.8	–11.2[c]	12.6	28.9	6.5	–16.7[b]	10.6	–13.3[b]	11.4
CGI-S	4.4	0.7	–0.9	1.1	–0.7	1.1	4.4	0.7	–1.5[b]	1.3	–1.0[c]	1.4	4.4	0.8	–1.6[b]	1.3	–1.2[b]	1.4
CGI-I	NA		3.0	1.1	3.3	1.2	NA		2.5[b]	1.2	3.0	1.5	NA		2.1[b]	1.0	2.6[b]	1.3
MRS	2.0	2.9	–0.6	4.0	–0.5	3.5	2.0	3.3	1.3[b]	6.0	0.9[c]	5.3	2.7	3.2	–0.8[d]	3.6	0.3	6.0

[a]Abbreviations: CGI-I = Clinical Global Impressions scale for Improvement, HAM-D = Hamilton Rating Scale for Depression, LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale, MRS = Mania Rating Scale, NA = not applicable.
[b]p < .05 vs. placebo.
[c]p < .1 vs. placebo.
[d]p < .1 vs. lamotrigine 50 mg/day.

Figure 2. Change From Baseline in Observed Scores at Each Treatment Visit Plus Week 7 LOCF Scores for 17-Item Hamilton Rating Scale for Depression (HAM-D), Item 1 (Depressed Mood) of the HAM-D, and MADRS



[a]Dose > 50 mg/day in lamotrigine 200-mg/d group only after week 3.
[b]p < .05 vs. placebo.
[c]p < .1 vs. placebo.

significantly reduced compared with placebo. LOCF scores were not significantly different from placebo for either active treatment dose.

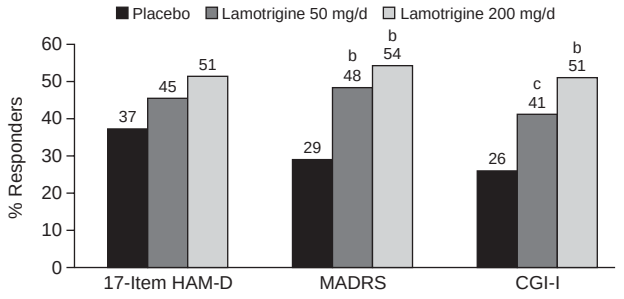
MADRS scores. Mean baseline MADRS scores were 28–29 ± 6–7 across treatment groups. Both lamotrigine 50-mg/day and lamotrigine 200-mg/day treatment resulted in mean 16- to 17-point reductions compared with the placebo reduction of 10 points (observed scores; see Table 4 and Figure 2). Improvement was significant by the third week of treatment and throughout the remainder of the study. LOCF analysis demonstrated statistically significant differences between lamotrigine 200 mg/day and placebo scores beginning at week 5; differences between lamotrigine 50 mg/day and placebo scores at the end of treatment approached significance (p = .058).

CGI-S scores. The mean ± SD baseline CGI-S score was 4.4 ± 0.7–0.8 (moderately to markedly ill) in each treatment group. CGI-S scores were significantly reduced compared with placebo by the end of treatment in the lamotrigine 200-mg/day group (observed and LOCF scores) and in the lamotrigine 50-mg/day group (observed scores) (see Table 4).

CGI-I scores. Mean CGI-I scores improved steadily with lamotrigine treatment; statistically significant differences in observed scores between both lamotrigine groups and placebo were observed by the third week and continued to the end of treatment (see Table 4). LOCF scores during weeks 4, 5, and 7 of treatment were significantly lower in the lamotrigine 200-mg/day group, but not the lamotrigine 50-mg/day group, compared with placebo.

Combined week 3 analysis. Since both lamotrigine groups received the same dosing for the first 3 weeks of treatment (≤ 50 mg/day), the first 3 weeks of data were analyzed comparing the entire population receiving lamotrigine (N = 127) with placebo. The lamotrigine-treated patients demonstrated significant improvements by week

Figure 3. Percentage of Patients Showing a Response to Treatment at Endpoint[a]



[a]Response defined as ≥ 50% reduction on the 17-Item HAM-D or MADRS scales or a rating of very much improved or much improved on the CGI-I scale.
[b]p < .05 vs. placebo.
[c]p <.1 vs. placebo.

3 ($p < .05$) on the following scales: HAM-D Item 1 (observed and LOCF scores), MADRS (observed and LOCF scores), CGI-I (observed scores), and CGI-S (observed scores).

Subgroup analysis. Results of each efficacy measure (17-item HAM-D, HAM-D Item 1, 31-item HAM-D, MADRS, CGI-S, and CGI-I) were compared between the 2 subgroups: patients with recent lithium use at minimally active levels (≥ 0.4 mmol/L or dosing of ≥ 600 mg/day for 1 month) during the 5 months preceding study entry and patients without such lithium use. There were no significant differences between the 2 subgroups on any of the efficacy measures. Furthermore, there was no significant effect of recent lithium use on the treatment group differences for any of the efficacy measures.

Responder analysis. Over 50% of the patients in the lamotrigine 200-mg/day group met the criteria for response to treatment by each of the following scales: 17-item HAM-D, MADRS, and CGI-I (Figure 3). The rate of response to lamotrigine 200 mg/day was statistically significant compared with placebo for both MADRS and CGI-I, whereas the rate of response to lamotrigine 50 mg/day was significantly higher than placebo only on the MADRS.

MRS scores. Mean ± SD baseline MRS scores were 2.0 ± 2.9 for the placebo group, 2.0 ± 3.3 for the lamotrigine 50-mg/day group, and 2.7 ± 3.2 for the lamotrigine 200-mg/day group. During treatment, mean changes in score were small and moved in both positive and negative directions. During treatment, groups did not differ significantly, with the exception that the placebo and lamotrigine 50-mg/day group observed scores demonstrated a reduction of 0.6 and a gain of 1.3, respectively, in MRS score on day 50 (see Table 4).

There were no significant differences between lamotrigine dose groups in efficacy scale change scores or responder rates at any treatment time.

Table 5. Most Common (≥ 5%) Adverse Events[a]

	Placebo (N = 65)		Lamotrigine 50 mg/day (N = 66)		Lamotrigine 200 mg/day[b] (N = 63)	
Adverse Event	N	%	N	%	N	%
Headache	11	17	23	35[c]	20	32[c]
Nausea	10	15	11	17	10	16
Pain	5	8	5	8	7	11
Rash	7	11	9	14	7	11
Dizziness	9	14	6	9	6	10
Accidental injury	2	3	1	2	6	10
Xerostomia	6	9	5	8	5	8
Manic/hypomanic/ mixed episodes	3	5	2	3	5	8[d]
Infection	9	14	4	6	4	6
Constipation	5	8	1	2	4	6
Diarrhea	10	15	3	5	3	5
Somnolence	8	12	3	5	3	5
Pruritus	4	6	7	11	3	5
Insomnia	6	9	5	8	2	3
Rhinitis	6	9	2	3	2	3
Influenza	4	6	1	2	2	3
Dyspepsia	4	6	3	5	1	2
Fatigue	4	6	3	5	1	2
Worsening of depression	1	2	4	6	0	0

[a]Patients reporting adverse events.
[b]Lamotrigine 200-mg/day group dose > 50 mg/day only after day 28.
[c]p < .05 vs. placebo.
[d]All but one event occurred during 25–50 mg/day dosing phase.

Compliance

In the placebo, lamotrigine 50-mg/day, and lamotrigine 200-mg/day dose groups, the majority (97%, 91%, and 97%, respectively) of the patients were over 70% compliant with medication dosing.

Adverse Events and Other Safety Data

Adverse events that emerged during the treatment phase and were experienced by 5% or more of patients in any treatment group are listed in Table 5. Ninety-two percent of placebo-treated patients reported any adverse event compared with 79% of patients in each lamotrigine group. The most common adverse event was headache, which was the only event observed significantly more frequently in the lamotrigine groups than the placebo group. Other common events were nausea, pain, rash, and dizziness. A smaller percentage of patients had any adverse events that were considered by investigators to be reasonably associated with study drug treatment (placebo, 60%; lamotrigine 50 mg/day, 54%; lamotrigine 200 mg/day, 51%).

There was one death in the placebo group on day 21 owing to probable suicide. Thirty-two other patients withdrew for adverse events (10 placebo, 12 lamotrigine 50 mg/day, and 10 lamotrigine 200 mg/day; see Table 1), including all of the serious adverse events described below. The adverse events accounting for more than one withdrawal included rash (2 placebo, 3 lamotrigine 50 mg/day, 4 lamotrigine 200 mg/day), a worsening of psychiatric de-

pression (1 placebo, 3 lamotrigine 50 mg/day), pruritus (1 placebo, 1 lamotrigine 200 mg/day), suicidal ideation (1 lamotrigine 50 mg/day, 1 lamotrigine 200 mg/day), suicide attempt (1 placebo, 1 lamotrigine 50 mg/day), and mania (2 lamotrigine 200 mg/day).

Nine patients experienced serious adverse events. Most of these events were related to bipolar disorder, including suicide (1 placebo), attempted suicide (1 placebo, 1 lamotrigine 50 mg/day), suicidal ideation (1 lamotrigine 50 mg/day, 1 lamotrigine 200 mg/day), worsening depression (1 lamotrigine 50 mg/day), and a psychotic episode (1 lamotrigine 50 mg/day). The illness-related events of 3 of the 4 patients in the lamotrigine 50-mg/day group (all but the attempted suicide) were the only serious adverse events considered to be possibly drug related. The other 2 events included a ruptured disk (placebo) and a myocardial infarction (lamotrigine 200 mg/day).

Rash was reported by 11% to 14% of patients in each treatment group (see Table 5). Rash led to withdrawal in 9 cases as noted above; the timing of these withdrawals ranged from 4 to 31 days after the start of treatment. None of the cases of rash were considered serious or resulted in hospitalization.

Manic, hypomanic, or mixed episodes were reported as adverse events in 10 patients (3 placebo [2 hypomania, 1 mixed], 2 lamotrigine 50 mg/day [1 hypomania, 1 mixed], 5 lamotrigine 200 mg/day [4 mania, 1 hypomania]; see Table 5), 2 of which led to withdrawal and none to hospitalization. In all but 1 of the 7 lamotrigine patients, these episodes occurred during the first 3 weeks of treatment when both lamotrigine groups were receiving 50 mg/day or less. The seventh patient's episode occurred on day 24, 3 days after the dose was increased to 100 mg/day. Overall, 7 (5.4%) of 129 patients on lamotrigine versus 3 (4.6%) of 65 patients on placebo developed these episodes ($p = .81$).

There were no apparent treatment group differences in clinical laboratory results postrandomization nor were there any patients with clinically significant changes in systolic blood pressure, diastolic blood pressure, pulse, or weight in any treatment group. Mean ± SD body weight at screening in the placebo, lamotrigine 50 mg/day, and lamotrigine 200 mg/day groups was 78.6 ± 16.0, 76.5 ± 17.6, and 82.2 ± 18.9 kg, respectively, and the mean change from screening to day 50 (LOCF scores) was 0.2, –0.4, and 0.0 kg, respectively.

DISCUSSION

This is the first randomized, parallel-group, placebo-controlled trial to evaluate any monotherapy treatment in bipolar I depression. The study results demonstrate that lamotrigine has significant antidepressant efficacy in bipolar I depression and that clinical improvement becomes evident as early as the third week of treatment.

Lamotrigine was significantly more effective than placebo on most, but not all, outcome measures. Patients receiving 200 mg daily exhibited significant improvement on all efficacy endpoints using both LOCF and observed case analyses, except the LOCF analysis of the 17-item HAM-D and both analyses of the 31-item HAM-D total score. Over 50% of patients given 200 mg daily met response criteria on the 17-item HAM-D, MADRS, and CGI-I. For MADRS and CGI-I, this rate of improvement was significantly higher and nearly twice that observed for those given placebo. Compared with the lamotrigine 200-mg/day group, the lamotrigine 50-mg/day group showed significant efficacy on fewer measures and the proportion of responders was somewhat lower.

These placebo-controlled data are consistent with the findings of earlier uncontrolled clinical reports of lamotrigine's efficacy in bipolar depression.[4–18] The largest of these previous studies[18] evaluated 40 depressed patients with either bipolar I or II disorder treated with lamotrigine as add-on therapy or monotherapy over 48 weeks. In it, Corn et al. reported a significant decrease in 17-item HAM-D scores over time compared with baseline and a 48% rate of marked response to lamotrigine.

The design of the current study provides significant advantages over previous studies of lamotrigine and other treatments for bipolar I depression. Published reports of other treatments for bipolar I depression include 9 studies (177 patients) of lithium,[25–33] one study (24 patients) of carbamazepine,[34] and 9 studies (466 patients) of marketed antidepressants.[25,35–42] Although most of these early innovative lithium studies suggest at least modest efficacy in bipolar depression, methodological problems limit interpretation of these data. Most of the studies did not limit enrollment to patients with bipolar depression, nor did the studies employ random assignment to parallel groups. The only efficacy analyses were of observed data (i.e., none employed LOCF analysis). Also, the use of lithium/placebo crossover designs may have confounded early estimates of lithium's antidepressant efficacy.[28,43] In the only double-blind study evaluating the antidepressant efficacy of carbamazepine, Post and colleagues[34] demonstrated significant improvement compared with placebo using a crossover design in a mixed cohort of bipolar and unipolar patients. Although the studies of marketed antidepressants used random assignment to parallel groups, they too had some methodological limitations. Only 6 limited enrollment to patients with bipolar disorder.[25,37,39–42] In contrast to the current study, 3 of these 6 studies permitted concurrent use of mood stabilizers[37,40,42] (2 standardized their use[40,42]), and most efficacy analyses were limited to observed data. These studies provided evidence for the efficacy of several classes of antidepressants, including nonselective monoamine reuptake inhibitors (imipramine, desipramine, bupropion),[25,39–41] selective serotonin reuptake inhibitors (fluoxetine, parox-

etine),[37,42] and MAO inhibitors (tranylcypromine, moclobemide)[38,39,41] when given alone or in combination with mood stabilizers.

Both lamotrigine treatment groups received the same doses of lamotrigine during the first 3 weeks of the study and first showed significant improvement over placebo during the third week when receiving 50 mg/day. Similar time to onset of antidepressant response has been reported for fluoxetine, tranylcypromine, and imipramine.[37,39] Comparisons with the rate of antidepressant response to lithium in bipolar I depression are not possible since the early lithium studies employed crossover designs rather than random assignment to a parallel placebo group.[25–33] Moreover, direct comparison studies would be needed to draw meaningful conclusions about onset of activity for lamotrigine relative to antidepressants or lithium.

Since this trial represents the first randomized, parallel-group, placebo-controlled trial to evaluate monotherapy treatment in bipolar I depression, there was no information available on placebo response rates in this population; the use of placebo was considered essential. The percentage of placebo patients with a response on the 17-item HAM-D in the current study (37%) is similar to that observed in the only other study of bipolar I depression employing random assignment to a parallel placebo group (38%).[37] The placebo-response rates for the MADRS and the CGI-I in our study were 29% and 26%, respectively; there are no previous reports using these 2 rating scales in a placebo-controlled bipolar depression trial. These rates of placebo response are roughly comparable to recently published unipolar depression studies[44,45] and will provide valuable benchmark data for future controlled studies in bipolar depression.

Lamotrigine was well tolerated in this study, and serious drug-related adverse events were uncommon. There was no difference between placebo and either dose of lamotrigine in the number of patients withdrawing from the study due to adverse events. The incidence of headache was higher in the lamotrigine groups compared with placebo; however, only 1 lamotrigine-treated patient was discontinued due to headache, one of several reasons given for discontinuation of this patient. The rates of other adverse events were similar to placebo for both doses of lamotrigine. The types of reported adverse events in this study are consistent with those previously reported for bipolar disorder patients by Corn and colleagues[18] as well as patients who received adjunctive or monotherapy lamotrigine for treatment of epilepsy.[46,47] Across the dose range tested there was no evidence of a dose-response relationship for adverse experiences. It is of interest to note that total adverse events and many of the reported CNS-related adverse events occurred numerically less frequently in the lamotrigine groups than in the placebo group.

The incidence of rash (11%–14%) was similar across placebo and lamotrigine groups and similar to that observed on lamotrigine treatment in open-label and placebo-controlled epilepsy clinical trials.[47,48] In 7 cases (5.4%), rash led to the discontinuation of lamotrigine. This frequency of rash-related withdrawal was similar to the rate for lamotrigine (6.1%) and lower than the rate for carbamazepine (8.9%) in previously reported lamotrigine active-control studies in epilepsy.[47] None of the rashes in the current study was considered serious or required hospitalization. In patients with epilepsy, the incidence of serious rash requiring hospitalization and discontinuation of treatment with lamotrigine has been reported to be approximately 3 in 1000 adults (1 in 100 in children ≤ 16 years old). These rashes usually occur within 8 weeks of the initiation of treatment.[48] There are suggestions, yet to be proven, that the risk of rash may be increased by coadministrating it with valproate, exceeding the recommended initial dose of lamotrigine, or exceeding the recommended dose escalation for lamotrigine.[48] Strict adherence to the recommended dose escalation schedule may diminish the likelihood of rash.

The current monotherapy study reported the rate of development of combined manic, hypomanic, or mixed episodes according to adverse event reports. The frequency of these combined mood episodes was not significantly different between lamotrigine and placebo groups. The event rate of 4.6%–5.4% in the current study that allowed no concurrent psychoactive medications compared favorably to the placebo switch rate of 3.3% in a study allowing concurrent lithium use.[37] In contrast, tricyclic antidepressants and MAO inhibitors evaluated in controlled monotherapy studies of the depressive phase of bipolar disorder suggest a higher rate of switching, as much as 25% for imipramine and 21% for tranylcypromine.[39] Direct comparison studies would be needed to draw meaningful conclusions about switch rates for lamotrigine relative to other antidepressants.

The design of this study had some limitations that could confound interpretation of the data. The fixed-dose titration schedule in this study resulted in both active treatment groups receiving the same dose for the first 3 weeks of the study. Hence, the 200-mg/day group reached target dose 2 weeks after the 50-mg/day group, and the groups had different durations of treatment at target dose (lamotrigine 50 mg/day: 5 weeks; lamotrigine 200 mg/day: 3 weeks). A longer duration for the blinded phase of the study would have lessened the impact of this difference and provided further information on the continued course of antidepressant response to lamotrigine. The ongoing open-label continuation phase of this study should help to address this limitation.

The MADRS appeared to separate efficacy differences between placebo and lamotrigine more robustly than the 17-item HAM-D. The 17-item HAM-D scale is weighted toward somatic symptomatology relative to the MADRS. These results suggest that effects on bipolar depression

(versus unipolar depression) may be more sensitively and reliably measured by scales that focus on nonsomatic depressive symptoms rather than those containing somatic items. Alternatively, effects of lamotrigine (versus other antidepressants) may be more sensitively and reliably measured by such scales.

The data from this first double-blind, placebo-controlled trial of lamotrigine monotherapy in bipolar disorder demonstrate that lamotrigine possesses significant antidepressant efficacy in bipolar I depression. In addition, the use of lamotrigine in patients with bipolar I depression was well tolerated, with a side effect profile similar to that of placebo.

Drug names: bupropion (Wellbutrin, Zyban), carbamazepine (Tegretol and others), chloral hydrate (Noctec), desipramine (Norpramin and others), fluoxetine (Prozac), imipramine (Tofranil and others), lamotrigine (Lamictal), lorazepam (Ativan and others), oxazepam (Serax and others), paroxetine (Paxil), temazepam (Restoril and others), tranylcypromine (Parnate).

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