A Single-Center, Double-Blind, Placebo-Controlled Evaluation of Lamotrigine in the Treatment of Obesity in Adults

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Received April 13, 2005; accepted Nov. 22, 2005. From the Affiliated Research Institute, San Diego, Calif.

This paper was supported by an investigator-initiated grant from GlaxoSmithKline, Research Triangle Park, N.C.

This paper was presented in part at the 158th annual meeting of the American Psychiatric Association, May 21–26, 2005, Atlanta, Ga.

Dr. Merideth reports no additional financial or other support.

The author acknowledges Steve Pashko, Ph.D.; Chris K. Southard, M.A.; Thomas Hochadel, Pharm.D.; and Christine K. Thomason, Ph.D., for their contributions.

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Objective: Unlike many pharmacotherapies for mood disorders, lamotrigine has not been shown to be associated with weight gain. This study evaluated the safety and efficacy of lamotrigine, compared with placebo, as a monotherapy for weight loss in obese adult subjects.

Method: Forty subjects were randomly assigned (1:1) to receive lamotrigine 200 mg/day or placebo for up to 26 weeks. Eligibility included a body mass index (BMI) of 30 to < 40. The primary endpoint was the change from baseline to endpoint (week 26) in subject weight. Secondary endpoints included the change from baseline to endpoint in BMI, percent body fat, serum lipid, and glycosylated hemoglobin values, subject satisfaction with treatment, and quality of life.

Results: Mean change in body weight from baseline to endpoint (last observation carried forward) was –6.4 ± 10.26 lb and –1.2 ± 7.09 lb for lamotrigine and placebo, respectively (p = .0623). Baseline body weight was slightly different between treatment groups (lamotrigine mean = 207.9 ± 19.88 lb, placebo mean = 225.0 ± 32.70 lb; p = .0588). There was a statistically significant difference (p = .0421) in mean change in BMI from baseline to endpoint (–1.5 ± 2.78 and –0.1 ± 1.05 for lamotrigine and placebo, respectively). Subjects were more satisfied with lamotrigine treatment compared with placebo (p = .0065). There were no significant differences between treatment groups in other secondary endpoints. The most frequently reported adverse event was mild-to-moderate headache, occurring in both treatment groups.

Conclusion: Lamotrigine demonstrated a statistically significant difference in mean change in BMI and a trend toward a decrease in body weight and was well tolerated.

(J Clin Psychiatry 2006;67:258–262)

Obesity is a common disorder, affecting over 97 million adults in the United States.[1] It is associated with increased morbidity through links with diabetes, hypertension, and heart disease, among many others. Loss of excess weight is associated with improvements in these comorbid conditions. Individual improvements in weight would aggregate to substantial improvements in the overall health of the United States as a whole.

Currently, there are only 2 pharmacologic options indicated for long-term (up to 2 years) weight management, orlistat and sibutramine, that have been approved by both the U.S. Food and Drug Administration (FDA) and European regulatory agencies. Orlistat is a pancreatic and lipase inhibitor that induces weight loss through the blockade of fat absorption and is recommended for people with a body mass index (BMI) ≥ 30 or BMI ≥ 27 in those who have other comorbidities.[2] However, this product is associated with an adverse event profile that includes a number of gastrointestinal events, such as oily spotting and fecal incontinence, that can limit its usefulness. Orlistat also has no effect on appetite. Sibutramine works by affecting appetite control centers in the brain, reducing food intake by increasing satiety. However, it has been linked to increases in blood pressure[3] and is contraindicated in patients with poorly controlled hypertension, coronary artery disease, arrhythmias, congestive heart failure, stroke, or severe hepatic or renal function impairment. Because of these factors, clinicians must resort to a limited variety of options beyond these 2 products, such as a recommendation for diet and exercise and dietary counseling. Additional weight loss products would provide physicians with needed new and effective options for treating obesity.

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Further, many medications used to treat mood disorders, including antipsychotics, antidepressants, and mood stabilizers, are associated with weight gain.[4,5] The antiepileptics lamotrigine and topiramate, however, have been shown to be weight neutral or associated with weight loss.[6–8] Topiramate has been associated with weight loss in patients with epilepsy[7,9] and bipolar disorder[10] and in otherwise healthy obese adults.[11] A review of 32 clinical trials in patients with epilepsy taking lamotrigine as adjunctive therapy or monotherapy (N = 463) showed no clinically significant weight change after at least 180 days of lamotrigine therapy, regardless of patient age or gender.[6] A similar pattern was noted by Biton et al.[8] in epileptic patients taking lamotrigine as monotherapy for 8 months. Lamotrigine is also not associated with weight gain in patients with bipolar disorder.[12]

Lamotrigine is an antiepileptic drug of the phenyltriazine class that is structurally and mechanistically distinct from other available antiepileptic drugs recently approved by the FDA for the maintenance treatment of adults with bipolar I disorder. Treatment options for patients with mood disorders that were not associated with unwanted weight gain would be advantageous.

The purpose of this study was to preliminarily evaluate the safety and efficacy of lamotrigine compared with placebo as a monotherapy treatment for weight loss in otherwise healthy but obese adult volunteers. Secondarily, this study assessed the effects of lamotrigine compared with placebo on BMI, percent body fat, subject quality of life and satisfaction, and blood lipid and glycosylated hemoglobin (HbA_{1c}) values.

If shown to be effective for weight loss in obese adult subjects, lamotrigine could be considered an additional option for treating obesity. This finding would be especially promising for patients with bipolar disorder, for which current treatments are often associated with weight gain.

METHOD AND PROCEDURES

Participants

Healthy adult volunteers (over the age of 18 years) were eligible to participate if they had a diagnosis of obesity as calculated by a BMI of ≥ 30 but < 40. This cutoff is consistent with guidelines proposed by the National Institutes of Health, in which obesity is defined by a BMI of 30 or greater.[1] Patients with a BMI of ≥ 40 are likely to seek treatments in addition to pharmacologic intervention and were not included in this study. Key exclusion criteria included insulin-dependent (type 1) diabetes, unstable or newly diagnosed type 2 diabetes, a history or current diagnosis of epilepsy, and any other medical condition that could contribute to weight change. Subjects with any Axis I psychiatric illness as confirmed by the Mini-International Neuropsychiatric Interview[13] at the screening visit were also excluded, as were patients with a history of treatment with lamotrigine; a history of skin rash, current skin rash, or a history of hospitalization for allergic reaction; or any implanted or nonremovable electronic device (e.g., pacemaker, pump).

Subjects were enrolled through referral as well as advertisements and were randomly assigned to treatment between August 2003 and May 2004. All subjects provided written informed consent after the procedures and possible side effects were fully explained and prior to the initiation of any study-related procedures. The study was conducted in accordance with the Declaration of Helsinki and was approved by a local institutional review board.

Procedures

Eligibility was assessed during a screening visit in which medical and psychiatric histories were reviewed and physical examination, electrocardiogram, and laboratory testing were conducted. Subjects meeting entry criteria were to return for a baseline visit within 2 weeks and were randomly assigned in a blinded manner (1:1 ratio) to receive lamotrigine 200 mg/day or placebo for 26 weeks. After screening and baseline visits, clinic visits were scheduled every 2 weeks until week 8, then again at week 13 and week 26, for a total of 8 visits. At each visit, vital signs including weight and height and percent body fat were measured, and information on adverse events and concomitant medications was collected. Additionally, subjects had 10 minutes to discuss "healthy living" with a study coordinator at each visit after screening. Materials on the importance of diet and exercise to weight loss and weight maintenance were made available for discussion.

Assessments of quality of life as measured by the Impact of Weight on Quality of Life (IWQOL)[14] scale and subject satisfaction with treatment (rated on a 5-point Likert scale with 1 = not satisfied and 5 = especially satisfied) were completed by subjects at baseline and endpoint (week 26). Safety assessments including a physical examination, electrocardiogram, and laboratory testing were completed again at the week 26 visit or if subjects discontinued participation in the study early. Subjects were discontinued from the study if a medically relevant adverse event or intercurrent illness occurred that posed a serious medical risk or if subjects experienced a rash (unless the rash was clearly not drug-related) or other signs and symptoms of a hypersensitivity reaction to study medication. Subject noncompliance with study procedures or inability to tolerate the minimum dose of study medication also prompted study discontinuation.

Dosing

All subjects received the same number of tablets (lamotrigine or placebo) for blinding purposes. Study medication was titrated to a maintenance dose level of between 150 and 200 mg/day. This is lower than the maintenance

dose for treatment of epilepsy recommended in the lamotrigine package labeling,[15] but consistent with recommended maintenance doses for the treatment of bipolar disorder. This dose was chosen based on the investigator's experience with previous lamotrigine studies and the more favorable tolerability profile associated with lower doses. Initial dosing for lamotrigine was at 25 mg/day for 2 weeks, then doubled every 2 weeks until the maximum dose was reached at week 6. Subjects who could not tolerate the maintenance dose were allowed a single dose decrease at any time on or after the week 6 visit to 150 mg/day. Subjects in the placebo group who experienced intolerance had their tablets decreased by an equivalent number to maintain the blind. Subjects who could not tolerate the decreased dose were withdrawn from the study. Once a subject had a dose decrease, the dose could not be subsequently increased.

Concomitant Medications

No psychoactive medications (including thyroid supplements) used to alleviate anxiety or depression were permitted during the study other than the short-term use of chloral hydrate, lorazepam (up to 1 mg/day), temazepam (up to 15 mg/day), or oxazepam (up to 30 mg/day) as needed for insomnia. Short-term use of medications with psychoactive ingredients such as cough or cold medicine was permitted as needed. Additionally, no subjects were taking medications that might affect weight (e.g., stimulants, appetite suppressants).

Data Analysis

The primary efficacy endpoint was defined as the change in body weight (in pounds) from baseline to endpoint (week 26). Analysis of covariance using change in body weight from baseline to week 26 as the dependent variable with treatment group as the predictor variable was completed using a last-observation-carried-forward (LOCF) approach. Body weight at baseline was used as a covariate. The intent-to-treat (ITT) population consisted of all subjects who were randomly assigned to study drug and who took at least 1 dose of study medication. The efficacy population consisted of all subjects in the ITT population with at least 1 postbaseline assessment.

Secondarily, treatment groups were also compared on change from baseline in BMI, percent body fat, IWQOL total score, subject satisfaction total score at the final visit, and HbA_{1c} and lipid panel values at all visits. Analysis methods for secondary endpoints were similar to the primary analysis.

RESULTS

Subject Characteristics

Of 57 subjects screened, 40 met entry criteria and were randomly assigned to treatment with lamotrigine (N = 20) or with placebo (N = 20). Of those who were randomly assigned, 28 completed the 26 weeks of treatment (17 taking lamotrigine, 11 taking placebo). Subject disposition and reasons for discontinuation are depicted in Figure 1. Subject demographics and baseline characteristics are noted in Table 1. A majority of subjects were women (82.5% [33/40]), and the subjects ranged in age from 23 to 65 years. Baseline body weight was slightly different between treatment groups (lamotrigine mean ± SD = 207.9 ± 19.88 lb, placebo mean ± SD = 225.0 ± 32.70 lb; p = .0588). Other baseline characteristics were similar between treatment groups.

All subjects taking lamotrigine were titrated to 200 mg/day, except 1 who was titrated to 100 mg and was dis-

Figure 1. Subject Disposition and Reasons for Discontinuation

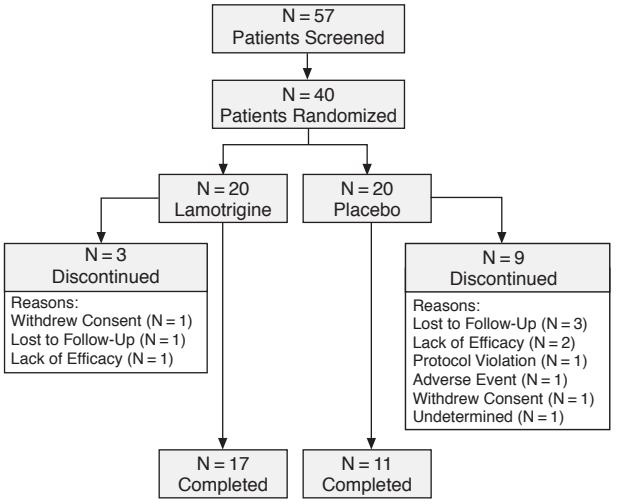


Table 1. Subject Demographics and Baseline Characteristics[a]

Characteristic	Lamotrigine (N = 20)	Placebo (N = 20)
Age, y	43.1 (11.6)[b]	41.9 (11.0)
Gender, N (%)		
Male	2 (10)	5 (25)
Female	18 (90)	15 (75)
Body weight, lb	207.9 (19.9)	225.0 (32.7)[c]
BMI	34.6 (2.6)	35.9 (3.3)
Body fat, %	44.3 (5.0)	42.5 (5.6)
HDL cholesterol, mg/dL	48.9 (11.9)	49.6 (12.8)
Cholesterol/HDL cholesterol ratio	4.4 (1.4)	4.1 (1.3)
Total cholesterol, mg/dL	209.7 (38.5)	192.0 (35.3)
LDL cholesterol, mg/dL	135.6 (34.4)	116.8 (28.2)
HbA_{1c}, %	5.2 (0.4)	5.4 (0.4)

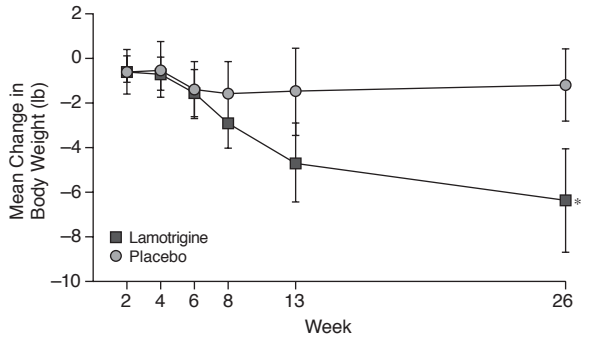
[a]Values are shown as mean (SD) unless otherwise noted. Baseline is defined as visit 1/screening.
[b]N = 19.
[c]p = .0588.
Abbreviations: BMI = body mass index, HbA_{1c} = glycosylated hemoglobin, HDL = high-density lipoprotein, LDL = low-density lipoprotein.

Table 2. Change in Efficacy Measures From Baseline to Endpoint (week 26, LOCF) in Obese Subjects Taking Lamotrigine or Placebo[a]

	Lamotrigine (N = 20)		Placebo (N = 20)		
Measure	Change From Baseline	% Change From Baseline	Change From Baseline	% Change From Baseline	p Value
Body weight, lb[b]	–6.4 (10.3)	–3.1 (5.0)	–1.2 (7.1)	–0.5 (2.8)	.0623
BMI[b]	–1.5 (2.8)	–4.4 (7.8)	–0.1 (1.1)	–0.4 (2.8)	.0421
Body fat, %[b]	–0.3 (3.6)	–0.2 (9.0)	–0.0 (1.9)	–0.2 (4.7)	.9836
HDL cholesterol, mg/dL[c]	–1.0 (6.1)	–1.2 (12.5)	–4.6 (9.0)	–7.9 (16.1)	.2157
Cholesterol/HDL cholesterol ratio[c]	–0.0 (0.7)	0.7 (18.6)	0.3 (0.8)	5.3 (19.3)	.3269
Total cholesterol, mg/dL[c]	–5.8 (20.9)	–2.1 (10.7)	–11.0 (29.0)	–4.9 (12.8)	.3323
LDL cholesterol, mg/dL[c]	–4.7 (18.0)	–3.0 (15.0)	–11.0 (23.4)	–8.3 (17.5)	.3169
HbA_{1c}, %[d]	0.1 (0.3)	1.8 (6.4)	0.0 (0.3)	0.4 (5.6)	.9093
IWQOL score[c]	–7.1 (15.9)	NA	–9.9 (11.3)	NA	.6744
Subject satisfaction[d,e]	0.0 (1.5)	NA	–1.4 (1.6)	NA	.0065

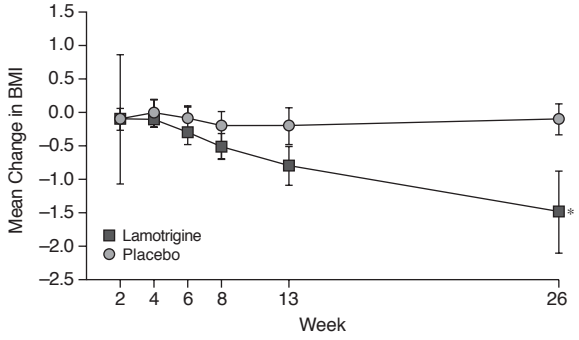
[a]Values are shown as mean (SD). Baseline is defined as visit 1/screening for all variables except IWQOL and subject satisfaction, for which baseline is defined as visit 2.
[b]N = 19 in the placebo group.
[c]N = 17 for lamotrigine, N = 14 for placebo.
[d]N = 18 for lamotrigine, N = 14 for placebo.
[e]Rated on a 5-point Likert scale on which 1 = not satisfied and 5 = especially satisfied.
Abbreviations: BMI = body mass index, HbA_{1c} = glycosylated hemoglobin, HDL = high-density lipoprotein, IWQOL = Impact of Weight on Quality of Life, LDL = low-density lipoprotein, LOCF = last observation carried forward, NA = not applicable.

Figure 2. Change From Baseline to Endpoint in Body Weight for Obese Subjects Taking Lamotrigine or Placebo[a]



[a]Bars represent standard error.
*p = .062.

Figure 3. Change From Baseline to Endpoint in Body Mass Index (BMI) for Obese Subjects Taking Lamotrigine or Placebo[a]



[a]Bars represent standard error.
*p = .042.

continued early. Both groups were compliant with taking medication (93% of medication was taken in subjects taking lamotrigine, 97% in those taking placebo).

Efficacy Results

Efficacy results are summarized in Table 2. Mean ± SD change in body weight from baseline to endpoint (LOCF) was –6.4 ± 10.26 lb and –1.2 ± 7.09 lb for lamotrigine and placebo, respectively (p = .0623), as depicted in Figure 2. There was a statistically significant difference in mean change in BMI from baseline to endpoint (–1.5 ± 2.78 and –0.1 ± 1.05 for lamotrigine and placebo, respectively; p = .0421), as shown in Figure 3. Subjects were also more satisfied with lamotrigine therapy compared with placebo (observed mean scores at endpoint were 3.7 ± 1.3 and 2.2 ± 1.3, respectively), and change from baseline in satisfaction scores was greater in the lamotrigine group (p = .0065). There were no significant differences between treatment groups in other secondary endpoints.

Safety Results

Only 1 subject taking placebo discontinued study medication due to an adverse event (edema). No subject taking lamotrigine was discontinued due to an adverse event. No serious adverse events were reported, and no serious safety concerns were observed. Adverse events re-

Table 3. Adverse Events Reported by ≥ 10% of Subjects in Either Treatment Group, N (%)

Adverse Event	Lamotrigine (N = 20)	Placebo (N = 20)
Headache	3 (15)	3 (15)
Rash	2 (10)	1 (5)
Bronchitis	2 (10)	0 (0)
Hives	2 (10)	0 (0)
Flu/cold symptoms	1 (5)	4 (20)

ported are noted in Table 3. The most frequently reported adverse event was mild-to-moderate headache, reported by 15% of those taking lamotrigine and 15% of those taking placebo. There were no differences of clinical importance between treatment groups on vital signs, physical examination findings, or electrocardiogram.

DISCUSSION

While there was no statistically significant difference in weight loss for those taking lamotrigine compared with those taking placebo, a trend was clearly noted ($p = .062$). Subjects taking lamotrigine experienced nearly 5 times the weight loss of those taking placebo. It is possible that this difference would have been statistically significant given a larger, more adequately powered study. However, despite the small sample size, a statistically significantly greater decrease in BMI was seen after 26 weeks of treatment with lamotrigine compared with placebo. Additionally, a longer study may have demonstrated a larger effect on weight loss; the trend noted in Figure 2 may have demonstrated continued divergence between groups with continued treatment beyond 26 weeks. These results were noted in a population that was otherwise healthy. For a psychiatric population, these results are particularly promising, as weight gain is often an associated side effect of psychotropic medication.

Lamotrigine was well tolerated in this study. Side effects reported were generally mild and transient (although dosing was lower than the maintenance dose for treatment of epilepsy but in the range for the treatment of bipolar disorder recommended in the lamotrigine package labeling[15]), and no subjects taking lamotrigine discontinued treatment due to an adverse event.

We do not yet have a clear understanding of the mechanisms involved in weight change. It is possible that lamotrigine may mediate an addiction response that in turn suppresses appetite. This idea is supported in studies that have shown lamotrigine to decrease drug cravings in patients with bipolar disorder and cocaine dependence.[16]

It should be emphasized that the results described here are promising in an otherwise healthy population in whom obesity is already a problem. In a setting where weight gain occurred secondary to pharmacotherapy (such as in patients with bipolar disorder initiating treatment with certain mood stabilizers), these results could be interpreted as simply a return to pretreatment or baseline condition. Future studies should include a larger sample, specifically in patients with bipolar disorder, to confirm a weight-neutral advantage for lamotrigine pharmacotherapy.

CONCLUSIONS

Lamotrigine demonstrated a statistically significant difference in mean change in BMI and a trend toward a decrease in body weight, with no negative impact on serum lipid or HbA_{1c} values. These preliminary results indicate that lamotrigine, unlike many pharmacologic treatments for bipolar disorder, is not associated with weight gain and may have some weight-reduction properties in obese subjects.

Drug names: lamotrigine (Lamictal), lorazepam (Ativan and others), orlistat (Xenical), sibutramine (Meridia), temazepam (Restoril and others), topiramate (Topamax).

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