

The Long-Term Impact of Mood Stabilizers on Body Weight

Gary Sachs, MD¹; Charles Merideth, MD²; Lawrence Ginsberg, MD³; Alan Swann, MD⁴; Thomas Thompson, MD⁵; Robin White, MS⁵; Connie Powers⁵

¹Harvard University, Boston, MA; ²Affiliated Research Institute, San Diego, CA; ³Red Oak Psychiatry, Houston, TX ⁴Univ. of Texas Health Science Center, Houston, TX; ⁵GlaxoSmithKline, NC

REVISED ABSTRACT

Introduction: Despite the availability of effective treatments for bipolar disorder, tolerability issues persist. Medication-related weight changes can negatively impact patient compliance with treatment.

Objective: To assess the long-term effect of lamotrigine on weight in patients with bipolar I disorder.

Methods: Weight data from 583 patients with bipolar I disorder in two long-term maintenance studies of lamotrigine (N=227), lithium (N=166), and placebo (N=190) were assessed. Analyses included observed mean weight change, proportion of patients with $\geq 7\%$ change in weight and weight-related adverse events (AEs), and a mixed model repeated measures analysis of weight change over time.

Results: Observed mean weight changes were negligible and were similar for subjects receiving lamotrigine and placebo; mean weight for patients on lithium increased over time. The proportion of subjects experiencing clinically important ($\geq 7\%$) weight changes and weight-related AEs were low and similar between the lamotrigine and placebo treatment groups. A mixed model repeated measures analysis showed that after one year of treatment, patients receiving lamotrigine and placebo had minimal mean weight changes (-1.2kg and +0.2kg, respectively) while patients receiving lithium experienced moderate weight gain (+2.2kg).

Conclusions: Long-term treatment with lamotrigine was not associated with clinically relevant changes in weight in patients with bipolar I disorder.

INTRODUCTION

Bipolar disorder is a chronic illness that requires long-term treatment for optimal management. Despite the availability of effective treatments, medication compliance issues persist due to unfavorable side effect profiles of some agents.

Weight gain is a specific area of concern for both clinicians and patients.^{1,2} One study conducted by Gitlin et al. evaluated the presence of side effects, the degree of distress, and the association of those side effects with treatment compliance on patients receiving lithium maintenance therapy for their bipolar disorder; and weight gain was reported as one of the most disturbing side effects to patients.³ Other agents (valproate, carbamazepine, gabapentin, olanzapine) used in the treatment of bipolar disorder are also commonly associated with weight gain.^{4,5,6}

Because weight can be a significant factor in overall tolerability and compliance with maintenance treatment for bipolar disorder, we examined the effects of up to 18 months of treatment with lamotrigine (LTG) therapy on body weight in the two 18-month trials which demonstrated the efficacy of lamotrigine in the maintenance treatment of Bipolar I Disorder.

METHODS

The two original studies were international protocols employing a maintenance design in which bipolar I patients who were, or had recently experienced a DSM-IV depressive (GW2003) or manic (GW2006) episode were enrolled.

Following IRB/Ethics Committee approval and written informed consent, symptomatic bipolar I patients were enrolled into one of two protocols. In each protocol, patients were entered into an 8 to 16 week, open-label preliminary study phase, during which lamotrigine was added to the patient's existing psychotropic regimen prior to gradual transition to lamotrigine monotherapy. Additionally, other drugs could have been added during the open label phase to control acute symptoms. Following stabilization, patients were randomized to monotherapy lamotrigine, lithium, or placebo.

Results were pooled; overall 583 patients were randomized to up to 18 months of double-blind treatment with lamotrigine (n=227, 100 to 400mg/day fixed and flexible dosing), lithium (n=166; 0.8 to 1.1mEq/L), or placebo (n=190).

This presentation focuses on the effect of lamotrigine on weight in patients with bipolar I disorder (up to 18 months of treatment).

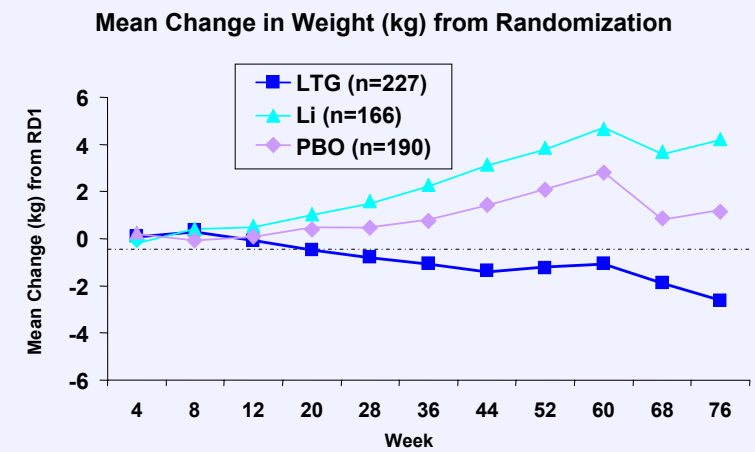
Measures

- Observed mean weight change measured at randomization and at Weeks 4, 8, 12, 20, 28, 36, 44, 52, 60, 68, and 76
- Proportion of patients with $\geq 7\%$ change in weight (at any time during the study from Randomization through Week 76)
- Weight-related AEs (at any time during the study from Screen through Week 76)
- Mixed model repeated measures (MMRM) analysis of weight change over time through Week 52

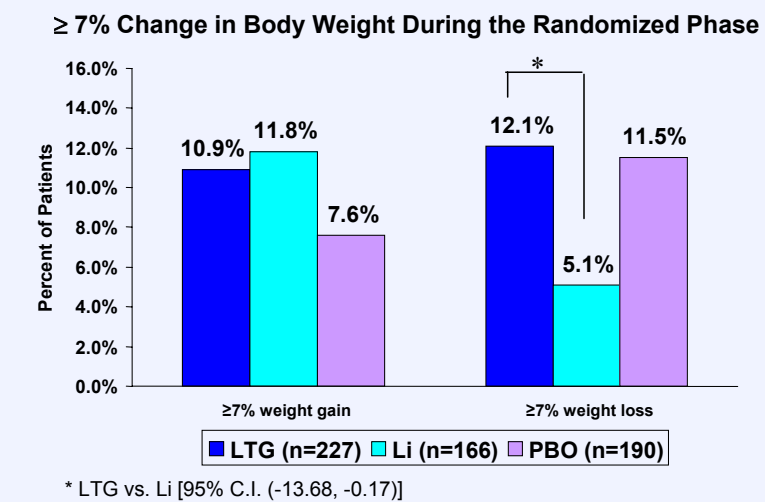
RESULTS

Patient Characteristics⁷

- ◆ Mean age = 43 years
- ◆ 55% female
- ◆ Mean weight at randomization was similar across treatment groups:
 - ◆ LTG = 79.8kg
 - ◆ Li = 80.4kg
 - ◆ PBO = 80.9kg
- ◆ 2/3 of patients had required psychiatric hospitalization in their lifetimes and 1/3 had a history of attempted suicide.
- ◆ Overall demographic and disease characteristics were comparable across treatment groups and indicative of moderate severity of illness.



- ◆ Over 18 months of treatment, patients treated with lamotrigine lost an average of -2.6 kg, patients treated with placebo gained +1.2kg, and patients treated with lithium gained +4.2 kg.

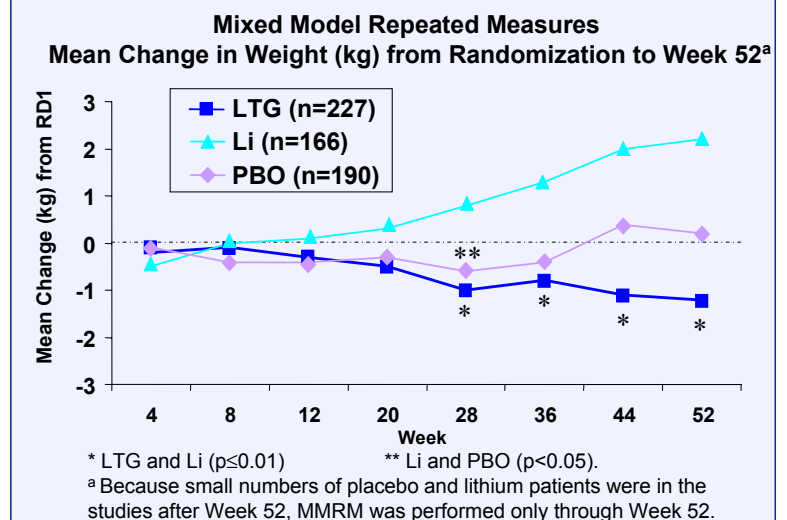


- ◆ There were no statistically significant differences between lamotrigine and placebo in the numbers of patients experiencing $\geq 7\%$ weight change, $\geq 7\%$ weight gain, or $\geq 7\%$ weight loss.
- ◆ More patients in the lamotrigine group experienced a $\geq 7\%$ weight loss (12.1%) compared to lithium (5.1%) [95% CI (-13.68, -0.17)].
- ◆ Lamotrigine patients were in the trial longer, which may have contributed to an increased chance of observing weight changes in the lamotrigine group (lamotrigine, lithium, and placebo treatment groups: 101, 70, and 57 patient years, respectively).

Percentage of Patients Reporting Weight-Related Adverse Events

	LTG	PBO	Li
Weight Gain	2	3	1
Weight Loss	<1	<1	0
Weight Fluctuation	0	0	<1

- ◆ Small percentages of patients reported weight gain, weight loss, or weight fluctuation as adverse events.



- ◆ No statistically significant differences were seen between the lamotrigine and placebo groups over the course of the study.
- ◆ Compared to placebo, lithium treated patients experienced statistically significant weight change from randomization at Week 28 (lithium: +0.8kg; placebo: -0.6kg).
- ◆ Statistically significant differences between lithium and lamotrigine were seen at Week 28 through Week 52 (lamotrigine: up to -1.2 kg; lithium: up to +2.2kg).

CONCLUSIONS

Long-term treatment with lamotrigine is not associated with clinically relevant changes in weight in patients with bipolar I disorder.

REFERENCES

1. Nemeroff CB. Safety of available agents used to treat bipolar disorder: Focus on weight gain. J Clin Psychiatry 2003; 64(5): 532-539.
2. Zarate CA. Antipsychotic drug side effect issues in bipolar manic patients. J Clin Psychiatry 2000. 61 Suppl 8:52-61; discussion 62-3.
3. Gitlin MJ, Cochran SD, Jamison KR. Maintenance lithium treatment: side effects and compliance. [comment]. J Clin Psychiatry. 1990 Mar; 51(3):126-7.
4. Sachs GS, Guille C. Weight gain associated with use of psychotropic medications. J Clin Psychiatry 1999; 60 (S21):16-9.
5. Devinsky O, Vuong A, Hammer A, Barrett PS. Stable weight during lamotrigine therapy: a review of 32 studies. Neurology 2000; 54:973-975.
6. Biton V, Mirza W, Montouris G, Vuong A, Hammer AE, Barrett PS. Weight change associated with valproate and lamotrigine monotherapy in patients with epilepsy. Neurology 2001; 56:172-177.
7. Goodwin GM, Phil D, Bowden CL, Calabrese JR, Grunze H, Kasper S, White R, Greene P, Leadbetter R. A Pooled Analysis of 2 Placebo-Controlled 18-Month Trials of Lamotrigine and Lithium Maintenance in Bipolar I Disorder. J Clin Psychiatry 2004; 65.