

Effects of Mood Stabilizers on Body Weight in Bipolar I Disorder

Lawrence Ginsberg, MD¹; Gary Sachs, MD²; Terence Ketter, MD³; Joseph Calabrese, MD⁴; Charles Bowden, MD⁵

¹Red Oak Psychiatry, Houston, TX; ²Harvard University, Boston, MA; ³Stanford University, Palo Alto, CA; ⁴Case Western Reserve University, Cleveland, OH; ⁵Univ. of Texas Health Science Center - San Antonio, San Antonio, TX

ABSTRACT

Objective: To examine the effects of mood stabilizers for bipolar I disorder on body weight.

Methods: 638 patients randomized to 18 months of double-blind monotherapy with lamotrigine (n=280; 50-400mg/day fixed and flexible dose), lithium (n=167; 0.8-1.1mEq) or placebo (n=191) were grouped by pretreatment body mass index (BMI): not obese = BMI < 30, obese = BMI ≥ 30. Mean observed change in body weight was examined through 52 weeks of treatment. Random effects mixed model with subject as a random effect and treatment, baseline weight, BMI category, visit, BMI category by visit interaction, treatment by visit interaction, and treatment by visit by BMI interaction as fixed effects was performed.

Results: After 52 weeks of treatment, mean change in body weight was significantly lower in the lamotrigine treatment group compared with placebo (p<0.02) and compared with lithium (p<0.0001). These differences were evident in both BMI categories, but were most evident in the obese category of patients: placebo + 1.46 kg, lithium +3.3 kg, and lamotrigine -2.96 kg.

Conclusions: Changes in body weight were correlated with choice of mood stabilizer and body mass index. Patients categorized as obese were at greatest risk for weight gain with lithium.

INTRODUCTION

Currently available therapies for bipolar disorder are effective for the prevention of mania and for acute control of mood episodes, however, they are associated with side effects that include significant weight gain. For example, recent studies of olanzapine in bipolar disorder have demonstrated weight gain of 7-11 pounds after only 3 weeks of treatment (Tohen et al. Am J Psych 2002; Zajecka et al. J Clin Psych 2002).

Individuals with bipolar disorder (BP) are particularly at risk for obesity, as the prevalence of obesity appears higher in this population and weight gain has been positively associated with the depressive phase of the illness. In fact, Fagiolini et al. (J Clin Psychiatry 2002) recently reported that the number of previous depressive episodes significantly contributed to the likelihood that patients with bipolar disorder were overweight or obese.

Lamotrigine (LTG) has demonstrated efficacy in the maintenance treatment of bipolar I disorder, predominantly at the depressive pole of the illness, in two large placebo- and lithium-controlled, 18-month clinical trials. We examined the effects of long-term lamotrigine and lithium maintenance therapy on body weight in these trials.

METHODS

GW2003 and GW2006 employed a relapse-prevention design with BP I patients who were currently, or had been recently depressed or manic (DSM-IV). Open-label LTG was administered for 8-16 weeks as add-on treatment. Patients with a positive treatment response were gradually withdrawn from their other psychotropic medications. Those reaching a stable LTG dose during the open-label phase and meeting response criteria (CGI-S score ≤3 X 4 weeks) were randomized to LTG flexible dosing (range 100-400mg/day) or fixed dosing (50, 200 or 400mg/day), lithium titrated to serum levels of 0.8-1.1 mEq/L, or placebo. (Note: The LTG 50mg/day group was eliminated from the final analyses based upon an hypothesis that the dose was sub-therapeutic.)

Results were pooled and 638 patients randomized to 18 months of double-blind monotherapy with lamotrigine (n=280; 50-400mg/day fixed and flexible dose), lithium (n=167; 0.8-1.1mEq) or placebo (n=191) were grouped by pretreatment body mass index (BMI): not obese = BMI < 30, obese = BMI ≥ 30.

Statistical Method: Mean observed change in body weight was examined through 52 weeks of treatment. Trends in body weight change continued through weeks 52 - 76, however, a decision was made not to include this portion of the data due to the potential effects of dropouts at these later time points.

A statistical model was built using the stepwise procedure to examine potential predictors of weight gain:

Age (> 35 vs. ≤ 35)	Gender
Race	Obesity (BMI < or >30)
HAMD (> 4 vs. < 4)	Score on HAMD item 17 (appetite)

Overall and by-treatment analyses were conducted by including parameters in the model one by one and then by applying the stepwise procedure. Covariates were included in the initial and final models at α=0.10, significant. Parameter effects were examined using a linear regression model.

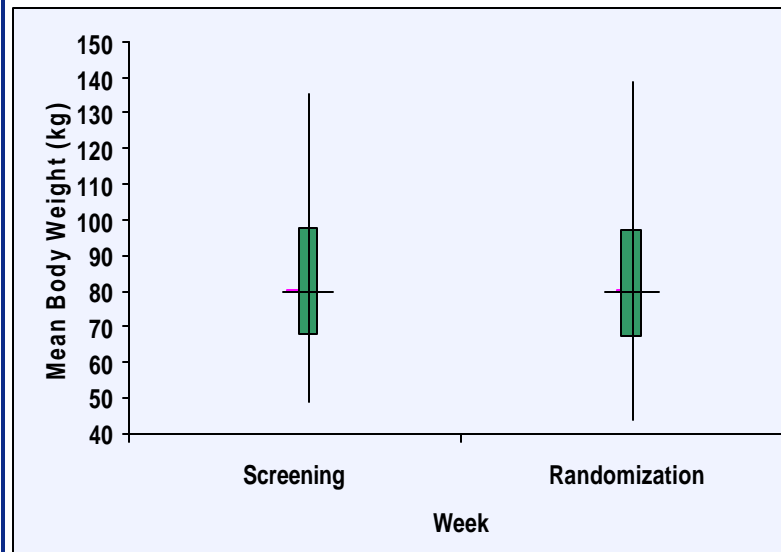
Random effects mixed model with subject as a random effect and treatment, baseline weight, obesity category, visit, obesity category by visit interaction, treatment by visit interaction, and treatment by visit by obesity interaction as fixed effects was performed.

RESULTS

Patient Characteristics

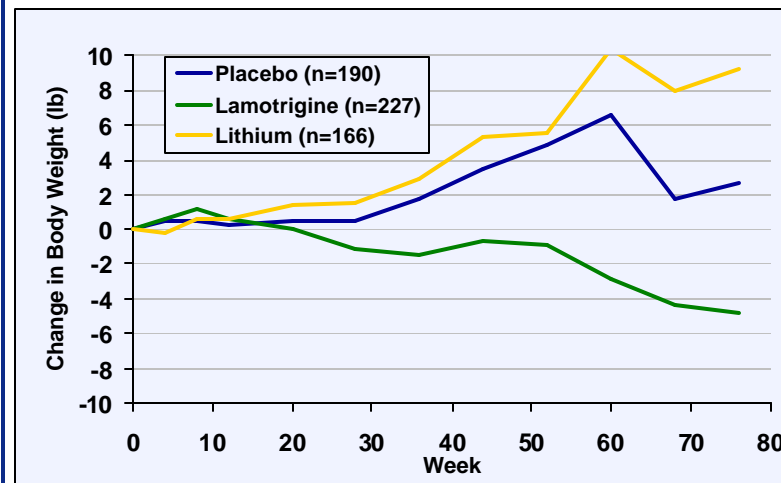
- ◆ Mean age = 42 years; 58% female.
- ◆ 2/3 of patients required psychiatric hospitalization in their lifetimes and 1/3 had a history of attempted suicide.
- ◆ Overall demographic and disease characteristics were comparable across treatment groups and indicative of moderate severity of illness.

Mean Observed Body Weight (LTG) Preliminary Phase (n=556)



** Lamotrigine as add-on therapy or monotherapy, on average, resulted in no change in mean body weight.

Mean Observed Change in Body Weight Randomized Phase

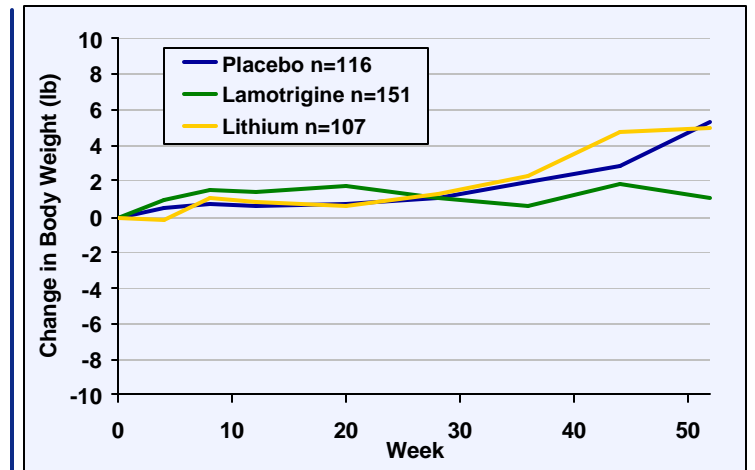


** Across 18 months of monotherapy, patients treated with lithium gained a mean of 9.3 lb; patients treated with lamotrigine lost an average of 4.8 lb.

Predictors of Weight Gain

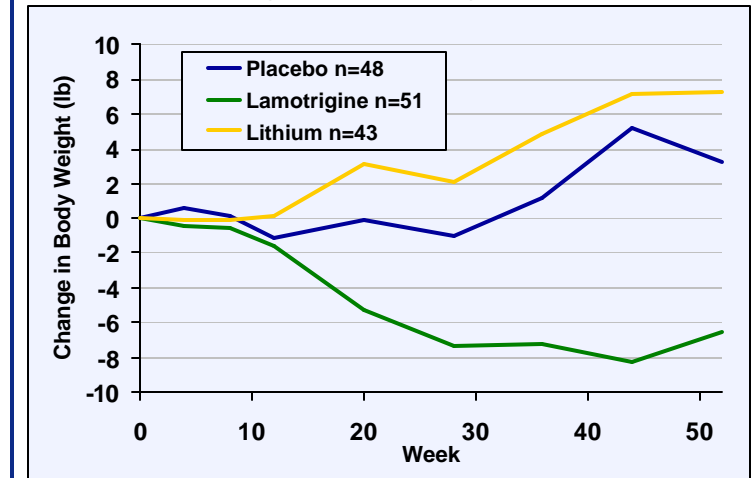
- ** BMI category predicted weight gain (p=0.10).
- ** Gender, age, race, median HAMD score, and HAMD score on item # 17 (appetite) were not predictive of weight gain.

Mean Change in Body Weight - BMI <30



** Non-obese patients did not gain significant weight after 1 year of LTG maintenance therapy.

Mean Change in Body Weight - BMI ≥30



◆ Obese patients who received PBO or Li gained weight (3.2 and 7.2 lb, respectively). Obese patients who received lamotrigine lost weight (-6.5 lb).

CONCLUSIONS

After 1 year of maintenance therapy for BPI:

- ◆ BMI category predicted weight gain.
- ◆ Changes in body weight varied by treatment and baseline BMI category (non-obese, obese).
- ◆ Patients who received lithium were at greatest risk for weight gain, regardless of baseline BMI category.
- ◆ Non-obese patients treated with lamotrigine did not gain weight. Obese patients treated with lamotrigine lost an average of -6.5 lb.