Adjunctive Maintenance Lamotrigine for Pediatric Bipolar I Disorder: A Placebo-Controlled, Randomized Withdrawal Study

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Objective: This study aimed to compare the efficacy of lamotrigine versus placebo in 10- to 17-year-olds with bipolar I disorder (BP-I) who were receiving conventional bipolar disorder treatment.

Method: In this randomized withdrawal trial, patients with BP-I of at least moderate severity received lamotrigine during an ≤18-week open-label phase. Patients who maintained a stable lamotrigine dose for ≥2 weeks and Clinical Global Impression–Bipolar Severity of Illness (CGI-BP[S]) score of ≤3 for ≥6 consecutive weeks were randomized to double-blind lamotrigine or placebo for ≤36 weeks.

Results: Of 301 patients enrolled, 298 comprised the open-label intention-to-treat population, with 173 (58%) randomized. Of these patients, 41 (24%) completed the study. In the open-label phase, the mean (SD) baseline CGI-BP(S) rating was 4.4 (0.57), and the mean (standard error [SE]) time to stabilization was 101 (1.6) days. During the randomized phase, mean (SE) time to occurrence of a bipolar event (TOBE) for lamotrigine versus placebo (primary endpoint) was 155 (14.7) versus 50 (3.8), 163 (12.2) versus 120 (12.2), and 136 (15.4) versus 107 (13.8) days for the 3 index mood states (depressed, manic/hypomanic, mixed). The primary stratified log-rank analysis of TOBE was not statistically significant (hazard ratio [HR] = 0.63; $p = .072$); however, the prespecified Cox regression analysis favored lamotrigine ($p = .047$). In 13- to 17-year-olds, log-rank analysis of TOBE significantly favored lamotrigine (HR = 0.46; $p = .015$), but not in 10- to 12-year-olds (HR = 0.93; $p = .877$). Dermatologic events were reported in 4% (open-label phase) and 2% (randomized phase) of patients receiving lamotrigine. Suicidality-related adverse events were reported in 7% (open-label phase) and 7% (randomized phase) of patients receiving lamotrigine.

Conclusion: Although the primary analysis failed to detect a benefit of add-on lamotrigine for BP-I in 10- to 17-year-olds, lamotrigine may be effective in a subset of older adolescents.

Clinical trial registration information—Lamictal as Add-on Treatment for Bipolar I Disorder in Pediatric Patients; http://clinicaltrials.gov/; NCT00723450.

Key words: lamotrigine, bipolar I disorder, pediatric, adolescent, adjunctive therapy

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Bipolar disorder (BD) is 1 of the most severe psychiatric illnesses, particularly in children and adolescents.[1] Childhood or adolescent onset is reported by approximately 50% to 65% of adults with BD.[2,3] The pediatric presentation of BD shares characteristics of severe adult BD, with rapid changes in mood (depression/mania), shorter periods of euthymia between mood episodes, and high rates of psychiatric comorbidity.[2,4,5] BD affects pediatric development and psychosocial functioning and increases the risk of suicide, substance use, and social problems.[6,7] Suicidal ideation and behavior are common in children and adolescents with BD.[8]

Lamotrigine, a sodium channel blocker and glutamate release inhibitor, was approved by the US Food and Drug Administration (FDA) in 2003 as maintenance treatment to delay time to occurrence of mood episodes in adults with bipolar I disorder (BP-I) receiving standard therapy for acute mood episodes.[9-12] Although lamotrigine is not approved in the United States for pediatric BD, published reviews have described lamotrigine use in pediatric patients (aged 4–17 years) with BD and other refractory mood disorders.[13-19] As monotherapy or combined with various psychoactive therapies, lamotrigine has been associated with improvements in rating scores for mania, and in the severity of symptoms of depression, attention-deficit/hyperactivity disorder (ADHD), and psychosis, with good tolerability in open-label studies and case reports.[13-19] Despite the lack of data from placebo-controlled trials, lamotrigine use for psychiatric treatment of pediatric patients increased significantly by 35.8% from 1996–1997 to 2008–2009 in the United States, and, in 2008–2009, proportionally represented 40.1% of anticonvulsant mood stabilizers used for psychiatric indications.[20] To address the lack of evidence-based studies in

Supplemental material cited in this article is available online.

this age group for BD, we have conducted the first multicenter study to evaluate adjunctive lamotrigine as a maintenance treatment for children and adolescents with BP-I.

METHOD

Study Design

A multicenter, parallel-group, placebo-controlled, double-blind, randomized withdrawal study (SCA102833/clinicaltrials.gov: NCT00723450) was conducted to evaluate the efficacy, safety, and tolerability of adjunctive lamotrigine (Lamictal, GlaxoSmithKline) in children and adolescents 10 to 17 years of age who were diagnosed with BP-I. Study phases were screening (~2 weeks), open-label (up to 18 weeks), and randomized (up to 36 weeks). In the randomized phase, patients received lamotrigine or placebo. Patients randomized to lamotrigine were continued on blinded doses of lamotrigine equivalent to the dose established in the open-label phase. Patients who were randomized to placebo were withdrawn from lamotrigine during the beginning of the randomized phase by means of a double-blind taper. Patients discontinuing from the study during the open-label phase entered an open-taper and follow-up phase that could last up to 4 weeks, depending on the dose of lamotrigine that the patient was receiving. Study treatment was supplied in identical blister cards (lamotrigine and placebo tablets matched). The study design is shown schematically in Figure 1.

Patients who met entry criteria during screening entered the open-label phase, during which the lamotrigine dose was titrated to maximal effectiveness, with the regimen dependent on the patient's age, weight (if applicable), and BD medication. Because of the inhibitory/inducer effects of certain BD medications on the metabolism of lamotrigine, patients were grouped as follows and dosages modified accordingly: valproate group, patients taking valproate; carbamazepine group, patients taking carbamazepine or any other enzyme-inducing drugs and not taking valproate; and neutral group, patients taking noninducer noninhibitor medications only. Lamotrigine dosing for patients 10 to 12 years of age (designated children) was determined by weight (total dose in mg/kg/day) and concomitant bipolar medication(s). Lamotrigine dosing for patients 13 to 17 years of age (designated as adolescents) was based on concomitant bipolar medication(s). Both regimens were generally based on FDA-approved guidelines for pediatric patients with epilepsy.[11] Safety and efficacy were evaluated regularly throughout the study.

Patients meeting stability criteria (i.e., maintenance of a Clinical Global Impressions–Bipolar Severity of Illness [CGI-BP(S)][21] score of ≤3 for at least 6 consecutive weeks) were randomized in a 1:1 ratio to either continued lamotrigine or to placebo, while maintaining a stable dose of their concomitant bipolar treatment(s) and ADHD medication(s), if applicable.

To ensure adherence with the study treatment, patients were instructed to return their blister cards, empty or with any unused investigational product, to the investigator at their next visit. A record of the supplies dispensed, taken, and returned was recorded at each visit. Patients who missed three or more consecutive days of investigational product during the study were considered nonadherent and withdrawn from the study.

Patients

Eligible patients 10 to 17 years of age had a diagnosis of BP-I according to the *DSM-IV-TR*[22] and as determined using the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS-PL),[23] administered by a physician who was board certified or board eligible in child and adolescent psychiatry. Patients were also experiencing a manic/hypomanic, depressed, or mixed-mood episode and had moderate disease severity (CGI-BP[S] score ≥4). Patients were excluded if diagnosed with a primary Axis I nonbipolar disorder (except ADHD, anxiety disorders, oppositional defiant disorder [ODD], or conduct disorder [CD] to ensure that the "real-world" BP-I population was reflected) or Axis II disorder, or if they posed a homicidal or suicidal threat. Patients with a history of rash that was serious, required hospitalization, or was related to the use of lamotrigine were also excluded. The study was conducted at 32 centers in the United States. Patients were enrolled from existing patient populations, patient referrals, and in response to institutional review board (IRB)–approved advertising at selected sites. Enrolled patients were on a stable regimen of 1 or 2 protocol-specified concomitant treatments for BD (mood stabilizers and/or antipsychotics). Patients could also be receiving psychostimulant(s) for ADHD. Conventional bipolar and ADHD treatments allowed during the trial are listed in Table S1, available online. Dosing of concomitant bipolar medication(s) could be adjusted downward for tolerability issues only during the open-label phase. Once a patient had achieved 4 weeks of mood stability, no further dose adjustments for bipolar or ADHD medications were allowed. All patients who completed or withdrew from the study were to have a follow-up visit at the end of either the open-label taper or the double-blind taper phase.

Ethics and IRB Approval

The study protocol and other relevant information were reviewed and approved by an IRB in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good

FIGURE 1 Study design.