Where Does Lamotrigine Fit in the Pharmacotherapy of Mood Disorders?

An Evidence-Based Appraisal

Joseph F. Goldberg, MD

The clinical trials evidence base with lamotrigine places it in an often poorly understood niche within psychopharmacology. Its demonstrated efficacy, based on FDA registration trials, is to prevent impending occurrences of new mood episodes—predominantly depressions, rather than manias—in people with bipolar I disorder. As a "mood stabilizer," it functions essentially as the mirror image of lithium, insofar as lithium has been shown to prevent highs more meaningfully than lows,[1] while lamotrigine prevents lows more effectively than highs.[2] Referring to medications such as lithium or lamotrigine broadly as "mood stabilizers" fails to capture this critical differential polarity effect, which Ketter and Calabrese[3] previously referred to as mood stabilization from "above" (ie, achieving sustained euthymia predominantly via antimanic efficacy) versus from "below" (ie, sustained euthymia resulting mainly from antidepressant effects) the baseline mood state.

This article aims to provide a succinct, practical overview of the evidence supporting lamotrigine's efficacy and to identify shortcomings of previous study designs. Many clinicians may be unaware of the clinical trials database that establishes lamotrigine's distinct efficacy profile, or may presume it has pharmacodynamic properties that may not necessarily be evident. Thus, an additional aim is to address the predilection among some clinicians to favor lamotrigine in clinical settings outside of its evidence base—perhaps driven partly by its generally favorable tolerability profile—such as first-line monotherapy for bipolar II depression, adjunctive therapy in major depressive disorder (MDD), or for individuals with mood instability or impulsive aggression in the absence of a formal history of manic or hypomanic episodes.

A noteworthy question at the outset involves how best to define a "therapeutic dose" of lamotrigine in non-treatment resistant samples, and what constitutes a *minimum effective dose* versus an optimal dose. In the industry-sponsored trials for acute bipolar depression,[4] 200 mg/d was chosen as a fixed target dose in 4 trials and 100–400 mg/d was a flexibly dosed target range in a fifth. Clinicians often identify 200 mg/d as a usual target dose based on the data from maintenance trials, but the possible acute efficacy of doses between 50–200 mg/d has not been formally evaluated.

Bipolar Mania

Early small single-site randomized comparisons of lamotrigine versus lithium[5] or olanzapine[6] suggested possible antimanic properties for lamotrigine; the latter of these studies included a somewhat faster lamotrigine dosing titration schedule than is now recognized, as well as nontrivial "rescue" dosing of lorazepam (mean daily dose of 2.5 mg/d). Two subsequent large, multisite industry-sponsored studies of lamotrigine in bipolar mania, both unpublished,[7,8] failed to affirm these observations and found no efficacy versus placebo. Whether this reflected an artifact of the necessarily gradual dose titration, or intrinsic lack of antimanic properties, remains uncertain. Despite these negative *acute* mania trials, a recent Cochrane review of lamotrigine versus placebo for maintenance treatment of bipolar disorder found a 33% reduction in the likelihood of recurrent mania (risk ratio = 0.67, 95% confidence interval [CI], 0.51 to 0.87),[9] leaving open the possibility that lamotrigine may nevertheless have at least some value to prevent bipolar mania.

There is no compelling evidence that lamotrigine *induces* mania. Notably, secondary analyses from randomized industry trials in acute bipolar depression found no greater likelihood for cycling from bipolar depression to mania with lamotrigine than for placebo.[10]

However, the presence of subthreshold or low-grade mania symptoms at baseline was

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associated with lesser overall efficacy with lamotrigine, and attenuated benefits versus placebo in forestalling a next mood episode.

Acute Bipolar Depression

Subsequent studies turned attention to acute bipolar depression, driven partly on mechanistic grounds (ie, Ketter and colleagues'[11] hypothesis that lamotrigine's antiglutamatergic [antiexcitatory] properties may have more activating/antidepressant effects than seen with GABAergic [proinhibitory] drugs). The first RCT in this area failed to separate from placebo on the a priori–defined primary outcome measure (the Hamilton Depression Rating Scale) using a last-observation-carried-forward analysis; however, significant improvement versus placebo was seen on a secondary outcome measure, the Montgomery-Asberg Depression Rating Scale (MADRS).[12] Four subsequent acute bipolar depression studies, each now adopting the MADRS as the primary outcome measure, failed to separate from placebo.[13] Importantly, a meta-analysis[13] found that lower baseline severity may have inflated the placebo response in each of those studies, likely producing a series of *failed* rather than *negative* trials. Collectively, but not individually, the industry-based trials of lamotrigine for acute bipolar depression did identify a signal for efficacy, with a modest number needed to treat of 13,[13] suggesting a fairly small magnitude of effect versus placebo.

Adjunctive Therapy

Conceptually, lamotrigine lends itself to combination therapies with virtually all psychotropic drugs (provided one takes into account relevant pharmacokinetic effects from UDP-glucuronosyltransferase inhibitors [such as valproate, requiring halving of a lamotrigine dose] or inducers [such as carbamazepine, requiring doubling of lamotrigine's dose]). Estrogen-containing contraceptives (similar to the pregnancy state) also induce lamotrigine's metabolism, potentially requiring lamotrigine dosage adjustments if breakthrough symptoms emerge. The literature contains only 2 dedicated studies of adjunctive lamotrigine therapy in bipolar depression. A first found superior antidepressant efficacy for lamotrigine plus lithium over lithium alone,[14] and a second showed greater antidepressant efficacy over 1 year with lamotrigine plus quetiapine than with quetiapine alone.[15]

Bipolar II Depression

In the manufacturer's FDA registration trials for bipolar depression, lamotrigine did not show greater efficacy than placebo in bipolar II disorder (owing, perhaps, to greater placebo-responsivity in bipolar II than bipolar I depression). A later single site outpatient randomized, placebo-controlled trial (n = 150) found potential value in melancholic but not non-melancholic bipolar II depression.[16] Some practice guidelines nevertheless advocate for the use of lamotrigine in bipolar II depression based on expert opinion despite the paucity of supportive clinical trial evidence.

Rapid Cycling

A 6-month industry-sponsored randomized trial in rapid cycling bipolar patients showed no advantage for lamotrigine over placebo in the primary outcome measure (time until the need for additional pharmacotherapy), although study retention was significantly longer with drug than placebo.[17] "Triple" mood stabilizer therapy (adding lamotrigine to divalproex and lithium) among rapid cycling patients with comorbid substance use disorders was found to be no better than dual therapy with divalproex plus lithium.[18]

Affective Instability

Moment-to-moment vicissitudes of mood are not part of the operational definition of bipolar disorder, but affective lability can occur in some if not many individuals with bipolar disorder.[19] In a post hoc analysis of the above-noted 6-month randomized trial in rapid cycling,[17] achievement of euthymic mood at least once per week was 1.8 times greater with lamotrigine than placebo.[20]

Sudden or abrupt shifts of mood are considered to be a nonpathognomomic, transdiagnostic phenomenon that can occur across a wide range of syndromes other than bipolar disorder, including borderline personality disorder, posttraumatic stress disorder (PTSD), developmental disorders, major cognitive disorders, major depressive disorder, and substance use disorders, among others.[19] Clinicians who may construe the idea of a "mood stabilizer" as a universal remedy for affective lability may be inclined to propose lamotrigine as a viable pharmacotherapy option for a wide range of patients who manifest abrupt shifts in mood from euthymia to irritability or anxiety, although data to support this perspective are sparse. Only 1 small preliminary randomized trial of lamotrigine in borderline personality disorder found that self-rated affective lability improved significantly better than with placebo,[21] a finding that was not replicated in a larger 1-year placebo-controlled trial.[22] A recent meta-analysis of lamotrigine in borderline personality disorder concluded that although the drug was well-tolerated, it was no different from placebo for treating core symptom domains of borderline personality disorder.[23]

Impulsive Aggression

Rage attacks and other forms of impulsive aggression or disruptive behavior constitute another nonpathognomic, transdiagnostic psychiatric phenomenon for which "mood stabilizers" such as lamotrigine are sometimes prescribed as a symptom-based treatment. Single case reports and small open trials in the literature propose that lamotrigine may be useful to counter impulsive aggression in patients with attention-deficit/hyperactivity disorder, PTSD,

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frontal lobe dementia, traumatic brain injury, schizophrenia, or temporal lobe epilepsy, but controlled trials are lacking. In individuals with borderline personality disorder, a secondary analysis of impulsive-aggression measures across 3 randomized trials found high heterogeneity and no significant difference from placebo with lamotrigine.[23]

(Unipolar) Major Depressive Disorder

Studies of lamotrigine adjunctive therapy in (unipolar) major depression are few in number, and findings have generally been disappointing. A small 6-week randomized comparison of lamotrigine (100 mg/d) or placebo cotherapy with fluoxetine (20 mg/d) in bipolar II (n = 8) or major depressive disorder (n = 15) found no treatment group differences in depression symptom severity score ratings (or outcome differences between unipolar and bipolar subjects) but did note significant improvement in clinical global impression scores.[24] However, a subsequent larger (n = 96) 10-week multisite trial of lamotrigine or placebo in major depression unresponsive to paroxetine and 1 prior antidepressant showed no advantage over placebo on any depression symptom severity scales, clinical global impression scores, or functional outcome scores.[25] A more recent small study of intravenous ketamine for treatment resistant depression (n = 11 unipolar, 2 = bipolar II disorder) found no significant advantage for adjunctive lamotrigine versus placebo.[26]

Summary

The existing clinical trials database for lamotrigine favors its utility in preventing (mainly depressive) recurrences in bipolar I disorder. It may best be viewed as a mood stabilizing agent with predominantly antidepressant properties—particularly as prophylaxis—with a therapeutic benefit that is less well-established either acutely or in patients with conditions other than bipolar I disorder. Design limitations of existing trials limit the extent to which its possible broader pharmacodynamic properties can be generalized or brought to bear as an evidence-based option in wider clinical populations with mood dysregulation.

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Author Affiliations: Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, New York.

Corresponding Author: Joseph F. Goldberg, MD, 128 East Ave, Norwalk, CT 06851 (joseph.goldberg@mssm.edu).

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