Lamotrigine in Psychiatric Disorders

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ABSTRACT

Objective: Owing to the prevalence of medication side effects and treatment resistance, prescribers often consider off-label uses of US Food and Drug Administration (FDA)–approved agents for the treatment of persistent symptoms. The authors review the available literature on the FDA-approved and non-FDA–approved uses of lamotrigine in adults with psychiatric disorders.

Data Sources: We used PubMed, MEDLINE, and a hand search of relevant literature to find studies published between 1990 and 2012 and available in English language. The following keywords were searched: *lamotrigine, psychiatric, mood disorders, depression, personality disorders, anxiety, schizophrenia, side effects,* and *rash.*

Study Selection: Data were selected from 29 randomized controlled trials (RCTs). When RCTs were not available, open-label trials (6), retrospective case reviews (10), and case series (4) were summarized.

Data Extraction: We extracted results of monotherapy and augmentation trials of lamotrigine on primary and secondary outcome measures.

Results: Lamotrigine is generally well tolerated, with the best evidence for the maintenance treatment of bipolar disorder, particularly in prevention of depressive episodes. In acute bipolar depression, meta-analyses suggested a modest benefit, especially for more severely depressed subjects, with switch rates similar to placebo. In unipolar depression, double-blind RCTs noted benefit on subsets of symptoms and improved response in more severely depressed subjects. Data are limited but promising in borderline personality disorder. Use of lamotrigine in schizophrenia and anxiety disorders has little supportive evidence.

Conclusions: Lamotrigine is recommended in bipolar maintenance when depression is prominent. It also has a role in treating acute bipolar depression and unipolar depression, though the latter warrants more research. Data are too limited in other psychiatric disorders to recommend its use at this time.

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Over the last 15 years, lamotrigine has achieved a central role as a pharmacotherapy for psychiatric disorders. It was first utilized off-label in 1986, with US Food and Drug Administration (FDA) approval for epilepsy in 1994 (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails). Its use in psychiatric illness emerged from the observation of mood improvement in subjects taking lamotrigine for partial epilepsy.[1] This discovery led to several controlled and uncontrolled studies examining its use in subjects with mood disorders, including bipolar disorder (acute mania, mixed and depressive episodes, maintenance treatment) and unipolar depression. Two randomized, placebo-controlled trials[2,3] demonstrated efficacy in preventing bipolar mood episodes, leading to lamotrigine's only psychiatric FDA indication, for bipolar maintenance treatment.

This article will review the literature on the FDA–approved and non-FDA–approved uses of lamotrigine in subjects with psychiatric disorders. Clinical trial data for mood disorders as well as other psychiatric disorders, including borderline personality disorder, schizophrenia, posttraumatic stress disorder (PTSD), obsessive-compulsive disorder, and panic disorder, will be discussed. Finally, a brief description of side effects, particularly rash, will be presented.

Basic Science/Mechanism of Action/Pharmacokinetics

Lamotrigine is a triazine derivative that inhibits voltage-sensitive sodium channels, leading to stabilization of neuronal membranes. It also blocks L-, N-, and P-type calcium channels and has weak 5-hydroxytryptamine-3 (5-HT_3) receptor inhibition.[4] These actions are thought to inhibit release of glutamate at cortical projections in the ventral striatum limbic areas.[5] It has nearly complete oral bioavailability, approximately 55% plasma protein binding,[4] and an absorption rate that is not influenced significantly by concomitant administration of food.[6]

Lamotrigine's half-life is 15–30 hours in the absence of enzyme inducers, such as phenobarbital, primidone, carbamazepine, and phenytoin, and 8–20 hours while patients are concurrently on these inducers.[4] Lamotrigine may induce its own metabolism.[4] Estrogen-containing contraceptives may also decrease serum concentrations of lamotrigine.[7] In addition, during pregnancy, lamotrigine clearance can increase significantly, with concentrations returning to baseline level just weeks after delivery.[8] Concurrent use with valproic acid prolongs lamotrigine's half-life to 30–90 hours.[7] Sertraline may also slow the metabolism of lamotrigine.[9] The main route of elimination is glucuronic acid conjugation to inactive metabolites, followed by excretion in the urine (94%, with 10% unchanged) and feces (2%).[4] Lamotrigine has no cytochrome P450 interactions but is a major 1A4 substrate as well as 2B7 in the UDP-glucuronosyltransferase system (second-phase metabolism).[4]

Some evidence suggests that lamotrigine may potentiate side effects of valproic acid, including tremor,[10] and can reduce the tolerability of carbamazepine when coadministered, causing central nervous system toxicity, with symptoms including diplopia and dizziness.[11] However, this latter effect, which appears to be pharmacodynamic, is more common when adding lamotrigine to high doses of carbamazepine

(serum concentrations > 8 mg/L) and usually resolves with a decrease in carbamazepine dose.[11]

DATA SOURCES

We used PubMed, MEDLINE, and a hand search of relevant literature to find studies between 1990 and 2012 and available in English language. The following keywords were searched: *lamotrigine, psychiatric, mood disorders, depression, personality disorders, anxiety, schizophrenia, side effects,* and *rash.*

STUDY SELECTION

Studies were selected on the basis of design, with preference given to double-blind, randomized controlled trials (RCTs) examining the use of lamotrigine as monotherapy or augmentation in psychiatric disorders. A total of 29 RCTs met this criterion. When RCTs were not available, open-label trials (6), retrospective case reviews (10), and case series (4) examining lamotrigine monotherapy or augmentation were summarized.

DATA EXTRACTION

The review includes results of monotherapy and augmentation trials of lamotrigine on primary and secondary outcome measures. These included *DSM-IV* diagnostic criteria, Hamilton Depression Rating Scale (HDRS), Montgomery-Asberg Depression Rating Scale (MADRS), Clinical Global Impressions (CGI), Young Mania Rating Scale (YMRS), Mania Rating Scale, Global Assessment of Functioning (GAF), Positive and Negative Syndrome Scale (PANSS), Brief Psychiatric Rating Scale (BPRS), and Duke Global Rating for PTSD Scale.

RESULTS

Mood Disorders

Bipolar disorder: acute hypomania/mania. There have been 2 unpublished double-blind, placebo-controlled studies of lamotrigine versus lithium in the treatment of acute mania and mixed episodes, with data discussed in a review by Amann et al.[12] Data from the first, 3-week comparator trial (SCAA2008) demonstrated no difference in either drug's separation from placebo on the primary outcome variable of change in Mania Rating Scale score from baseline to day 22. In the second, 6-week trial (SCAA2009) lithium, but not lamotrigine, was superior to placebo in change in Mania Rating Scale scores from baseline to day 42. Given this negative trial and the length of time for titration up to a therapeutic dose, lamotrigine is not a drug of choice for the acute treatment of mania.

Bipolar disorder: acute depression.

Monotherapy. Table 1 presents the double-blind, randomized trials of lamotrigine monotherapy for bipolar depression. Trials have included both bipolar I and II disorders, depressed episodes. In the first RCT of lamotrigine, Calabrese et al[13] performed a double-blind, parallel-group, multicenter trial of subjects with bipolar I depression. Subjects with a 17-item HDRS score ≥ 18 were randomized to treatment with a target dose of lamotrigine 50 mg/d (n = 66), lamotrigine 200 mg/d (n = 63), or placebo (n = 66). After 7 weeks of treatment, outcome of subjects taking lamotrigine 200 mg/d did not differ from placebo on the primary outcome measure, total HDRS score, and, therefore, this study was a negative trial. However, on secondary measures, lamotrigine 200 mg/d had a significantly superior response rate on mean ± SD observed scores on 17-item HDRS (−13.2 ± 7.4 [lamotrigine] vs −9.3 ± 6.9 [placebo], $P < .05$) and on last observation carried forward (LOCF) scores on the MADRS (−13.3 ± 11.4 [lamotrigine] vs −7.8 ± 10.4 [placebo], $P < .05$), CGI-Severity of Illness (−1.2 ± 1.4 [lamotrigine] vs 0.7 ± 1.1 [placebo], $P < .05$), and CGI-Improvement (2.6 ± 1.3 [lamotrigine] vs 3.3 ± 1.2 [placebo], $P < .05$).

A second article by Calabrese et al[14] summarized the results of their previous work[13] together with 4 double-blind, placebo-controlled, parallel-group RCTs (GW603/SCAA2010,[14] SCA40910,[14] SCA100223,[14] and SCA30924[14]) of lamotrigine monotherapy for acute bipolar depression. Subjects in study GW603/SCAA2010[14] were diagnosed with either bipolar I or II disorder and were treated with lamotrigine doses ranging from 100 to 400 mg/d or placebo. Subjects in the other 4 studies were diagnosed with either bipolar I disorder (Calabrese et al,[13] SCA40910,[14] and SCA30924[14]) or bipolar II disorder (SCA100223[14]) and treated with lamotrigine doses fixed at 200 mg/d or placebo. (Calabrese et al[13] included a group on lamotrigine 50 mg/d, but these data were not included in the analyses performed by Calabrese et al[14] or reviewed here.) Subjects taking lamotrigine did not differ in response from those taking placebo according to the 17-item HDRS total scores or the MADRS, with the exception of 1 trial[13] (MADRS responders: 54% versus 29%, $P < .05$). The percentage of responders as assessed by CGI-Improvement score was significantly greater with lamotrigine in 2 studies (SCA100223[14] and Calabrese et al[13]), with 51% responding versus 26% responding ($P < .05$) and 61% versus 45% responding ($P < .05$), respectively. We found no reports of serious rash across all studies. Also, the incidence of all mania (ie, mania, hypomania, mixed episodes) across all studies was low and did not differ significantly between lamotrigine and placebo.

Interestingly, in a meta-analysis and meta-regression[15] on individual patient data (N = 1,072) from these 5 RCTs,[13,14] lamotrigine subjects were more likely than placebo subjects to respond to treatment as assessed by both HDRS (pooled

Clinical Points

- Lamotrigine is approved by the US Food and Drug Administration for the maintenance treatment of bipolar disorder and is particularly useful in preventing depression.
- Data also suggest a role in the treatment of acute bipolar depression.
- Lamotrigine is generally well tolerated, with headache, nausea, and mild rash occurring most commonly, while severe rash is estimated to occur in less than 0.2% of cases.

Table 1. Lamotrigine Monotherapy for Bipolar Depression

Reference	Method	Diagnosis	Daily Dose	N	Length, wk	Results
Calabrese et al, 1999[13]	Randomized, double-blind, placebo-controlled, parallel-group	Bipolar I depression	Lamotrigine: 50 mg, 200 mg	195	7	200-mg Dose superior to placebo on 17-item HDRS, MADRS, CGI-S, CGI-I
Calabrese et al, 2008[14] (SCAA2010)	Randomized, double-blind, placebo-controlled, parallel-group	Bipolar I or II depression	Lamotrigine: 100–400 mg	206	10	No difference in response via 17-item HDRS
Calabrese et al, 2008[14] (SCA40910)	Randomized, double-blind, placebo-controlled, parallel-group	Bipolar I depression	Lamotrigine: 200 mg	257	8	No difference in response via MADRS
Calabrese et al, 2008[14] (SCA100223)	Randomized, double-blind, placebo-controlled, parallel-group	Bipolar II depression	Lamotrigine: 200 mg	221	8	Lamotrigine superior response on CGI-I No difference via MADRS
Calabrese et al, 2008[14] (SCA30924)	Randomized, double-blind, placebo-controlled, parallel-group	Bipolar I depression	Lamotrigine: 200 mg	259	8	No difference in response via MADRS
Frye et al, 2000[16]	Randomized, double-blind, placebo-controlled, crossover (vs gabapentin)	Bipolar I or II depression or unipolar depression	Lamotrigine: ≤ 500 mg Gabapentin: ≤ 4,800 mg	31	18	52% (16/31) Response to lamotrigine on CGI Superior to gabapentin and placebo
Brown et al, 2006[17]	Randomized, double-blind, parallel-group (vs olanzapine-fluoxetine combination)	Bipolar I depression	Lamotrigine: ≤ 200 mg olanzapine-fluoxetine combination: 6/25, 6/50, 12/25, 12/50 mg	410	7	Olanzapine-fluoxetine combination superior on CGI-S, MADRS, and YMRS, but lamotrigine better tolerated
Brown et al, 2009[18]	Randomized, double-blind, parallel-group (vs olanzapine-fluoxetine combination)	Bipolar I depression	Lamotrigine: ≤ 200 mg olanzapine-fluoxetine combination: 6/25, 6/50, 12/25, 12/50 mg	410	25	Olanzapine-fluoxetine combination superior improvement on CGI-S, MADRS, and YMRS, but no difference in response or remission rates, relapse of patients in remission, or treatment-emergent mania

Abbreviations: CGI = Clinical Global Impressions Scale, CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, HDRS = Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, YMRS: Young Mania Rating Scale.

relative risk [RR] = 1.27; 95% CI, 1.09–1.47) and MADRS (pooled RR = 1.22; 95% CI, 1.06–1.41). Subjects taking lamotrigine also had significantly higher remission rates on MADRS (pooled RR = 1.21; 95% CI, 1.03–1.42). The numbers needed to treat (NNTs) were 11 (95% CI, 7–25) on the HDRS and 13 (95% CI, 7–33) on the MADRS, which are at the limits of clinical significance. No difference was found between lamotrigine and placebo on discontinuation rates (RR = 1.02; 95% CI, 0.93–1.11; $P = .731$). On exploratory subgroup analysis, with groups divided by severity based on baseline HDRS score of ≤ 24 versus > 24, lamotrigine was superior to placebo only in individuals with more severe depressive symptoms at randomization (RR = 1.47; 95% CI, 1.16–1.87; $P = .001$). However, as the authors note, the interaction by severity was most likely due to a higher placebo response rate in the moderately ill group rather than a higher response rate to lamotrigine in the severely ill group.

In a double-blind, 18-week, crossover RCT[16] of gabapentin versus lamotrigine versus placebo in 31 subjects with refractory bipolar and unipolar mood disorders, subjects were blindly titrated to clinical efficacy or maximum tolerated dose of each (lamotrigine, ≤ 500 mg/d; gabapentin, ≤ 4,800 mg/d) or placebo. The response rates on CGI for Bipolar Illness overall were as follows: 52% for lamotrigine, 26% for gabapentin, and 23% for placebo (Cochran's $Q_2 = 6.952$, N = 31, $P = .031$).

Brown and colleagues[17,18] published data from an acute, 7-week trial and 6-month follow-up of olanzapine-fluoxetine combination versus lamotrigine in bipolar I depression. Results indicated greater symptom improvement on olanzapine-fluoxetine combination than lamotrigine on primary outcome measures, including CGI-Severity of Illness, MADRS, and YMRS scores at both 7 weeks and 25 weeks. However, neither response rates nor remission rates differed significantly between the groups at 25 weeks. Of the subjects in remission at the end of the 7-week acute phase (olanzapine-fluoxetine combination [56.4%] vs lamotrigine [49.2%], $P = .158$), the rate of relapse did not differ significantly between the groups (olanzapine-fluoxetine combination [13/95 = 13.7%] vs lamotrigine [14/77 = 18.2%], $P = .528$). Additionally, subjects taking olanzapine-fluoxetine combination had more frequent occurrences of somnolence, increased appetite, dry mouth, sedation, weight gain, and tremor ($P < .05$). Also seen was a significantly increased incidence of treatment-emergent cholesterol level ≥ 240 mg/dL, increased levels of triglycerides and prolactin, and weight gain of ≥ 7% in the olanzapine-fluoxetine combination group (all P values < .001).

Bipolar depression augmentation. Several studies have explored the use of lamotrigine as an augmentation agent for breakthrough bipolar disorder with depressive episodes not responsive to typical mood stabilizers. Table 2 presents the studies for lamotrigine as an augmenting agent for bipolar and unipolar depression. Schaffer et al[19] performed a randomized, double-blind, 7-week pilot trial of lamotrigine versus citalopram augmentation for bipolar I and II

Table 2. Lamotrigine Augmentation for Depression: Bipolar or Unipolar Major Depressive Disorder

Reference	Method	Diagnosis	Daily Dose	N	Length	Results
Nierenberg et al, 2006[20]	Randomized, open-label, equipoise-stratified	Bipolar I or II depression	Lamotrigine: 150–250 mg Risperdal: ≤ 6 mg Inositol: 10–25 g	66	16 wk	Lamotrigine subjects in study significantly longer Recovery: lamotrigine, 23.8% (5/21), vs inositol, 17.4% (4/23), vs Risperdal, 4.6% (1/22) (not significant)
van der Loos et al, 2009[21]	Randomized, double-blind, placebo-controlled (concurrent lithium)	Bipolar I or II depression	Lamotrigine: ≤ 200 mg Lithium: 0.6–1.2 mEq/L	124	8 wk	Lamotrigine with significantly more responders (51%) (33/64) on MADRS but not CGI-Bipolar
van der Loos et al, 2010[22]	Randomized, double-blind, placebo-controlled (concurrent lithium)	Bipolar I or II depression	Lamotrigine: ≤ 200 mg Lithium: 0.6–1.2 mEq/L Paroxetine: 20 mg	124	8 wk	No significant difference between lamotrigine and placebo groups after paroxetine augmentation
van der Loos et al, 2011[23]	Randomized, double-blind, placebo-controlled (concurrent lithium)	Bipolar I or II depression	Lamotrigine: ≤ 200 mg Lithium: 0.6–1.2 mEq/L Paroxetine: 20 mg	124	68 wk	Longer time to relapse or recurrence in lamotrigine group (10.0 mo) vs placebo (3.5 mo)
Norman et al, 2002[32]	Randomized, double-blind, placebo-controlled (concurrent paroxetine)	Unipolar depression, bipolar I or II depression	Lamotrigine: 200 mg Paroxetine: 40 mg	40	9 wk	No difference in total HDRS improvement, but superior to placebo on CGI-S and HDRS subitems
Barbosa et al, 2003[33]	Randomized, double-blind, placebo-controlled (concurrent fluoxetine)	Unipolar depression or bipolar II depression	Lamotrigine: ≤ 100 mg Fluoxetine: 20 mg	23	6 wk	Superior to placebo on CGI-S and CGI-I but not MADRS, HDRS
Barbee et al, 2011[34]	Randomized, double-blind, placebo-controlled (concurrent paroxetine)	Unipolar depression	Lamotrigine: 100–400 mg Paroxetine: 20–50 mg Paroxetine controlled release: 25–62.5 mg	96	10 wk	Trend ($P = .06$) for lamotrigine superiority in more severely depressed and treatment-resistant subgroup
Schaffer et al, 2006[19]	Randomized, double-blind, pilot (vs citalopram)	Bipolar I or II depression	Lamotrigine: ≤ 200 mg Citalopram: ≤ 50 mg	20	12 wk	Both with significant improvement on MADRS scores No difference between groups
Schindler et al, 2004[35]	Open-label, observational, comparative (vs lithium)	Unipolar depression	NA	40	8 wk	Equally effective in HDRS improvement Lamotrigine better tolerated
Rybakowski et al, 2006[37]	Open-label, comparative (vs lithium)	Unipolar depression or bipolar depression	NA	42	4 wk	Similar HDRS response with lamotrigine and lithium augmentation
Schindler et al, 2007[36]	Randomized, open-label, prospective, comparative (vs lithium)	Unipolar depression	Lamotrigine: mean, 153 mg Lithium: mean, 0.71 mEq/L	34	8 wk	Comparable to lithium augmentation on response and remission
Ivkovic et al, 2009[38]	Open-label, flexible dosing, comparative (vs lithium)	Unipolar depression	Lamotrigine: 5–500 mg Lithium: 600–1,200 mg	88	8 wk	Similar HDRS reduction, but lamotrigine superior to lithium at 14 d
Baloescu et al, 2006[39]	Open-label study	Unipolar depression	NA	16	4 wk	25% decrease in HDRS scores at 4 wk
Dimellis and Kouniakis, 2004[40]	Randomized, open-label comparison (lamotrigine plus sertraline vs increased sertraline)	Unipolar depression	NA	21	6 wk	Superior to higher dose sertraline on CGI scale but not HDRS
Gabriel et al, 2006[41]	Open-label, descriptive study	Unipolar depression	Lamotrigine: 50–200 mg	14	6 mo	Significant improvement on CGI-S, MADRS, and GAF at 8 wk and 6 mo
Barbee et al, 2002[42]	Retrospective chart review	Unipolar depression	Lamotrigine: mean, 112.9 mg	37	6 wk	40.5% (15/37) CGI response rate
Rocha et al, 2003[43]	Retrospective chart review	Unipolar depression	Lamotrigine: 200 mg	25	6 wk	76% (19/25) Improved on CGI
Gutierrez et al, 2005[44]	Retrospective chart review	Unipolar depression	Lamotrigine: 5 mg–500 mg	34	12 mo	Superior to placebo on multiple subscale items

Abbreviations: CGI = Clinical Global Impressions Scale, CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness, HDRS = Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, NA = not applicable, YMRS = Young Mania Rating Scale.

depression. A total of 20 subjects taking 1 or more mood stabilizers were randomized to either citalopram (up to 50 mg/d) or lamotrigine (up to 200 mg/d). Reduction in total MADRS score was significant for both lamotrigine (−13.3, $P = .001$) and citalopram (−14.2, $P = .002$). No statistically significant differences were found in response rates between the 2 groups.

In a 16-week, randomized, equipoise-stratified study[20] comparing lamotrigine, risperidone, and inositol in 66 subjects with bipolar I or II disorder in a current major depressive episode, no statistically significant differences were found between groups on the primary outcome measure, rate of recovery. However, those assigned to lamotrigine stayed in the randomized phase significantly longer (mean ± SD = 12.2 ± 7.9 weeks) than those assigned to inositol (5.8 ± 5.1 weeks) or risperidone (8.6 ± 4.9 weeks).

Lamotrigine was added to lithium in subjects who had not yet responded to lithium, targeting bipolar depression in an 8-week, multicenter, double-blind, randomized, placebo-controlled trial[21] of 124 outpatient subjects with a *DSM-IV* diagnosis of bipolar I or II disorder and a major depressive episode. This study was not designed to compare lamotrigine to lithium monotherapy directly but rather to assess efficacy of lithium plus lamotrigine in the treatment of acute bipolar depression. Significant differences were seen in change in MADRS score between the groups (lamotrigine, −15.38, standard error [SE] = 1.32; placebo, −11.03, SE = 1.36; $t_4 = -2.29$, $P = .024$). Additionally, significantly more subjects responded to lamotrigine (51%) than placebo (31.7%) ($P = .030$). No significant difference was found in switch to mania between the groups (lamotrigine, 7.8%; placebo, 3.3%; $P = .441$).

Following this initial 8-week trial, paroxetine 20 mg/d was added to nonresponders, and subjects were followed for 8 weeks[22] and up to 68 weeks[23] (or until relapse or recurrence of mood episode). Notable differences in the groups at 68 weeks included a higher percentage of subjects in the lamotrigine group remaining responders and a longer median time to relapse or recurrence for the lamotrigine group versus placebo (10.0 months [95% CI, 1.1–18.8] vs 3.5 months [95% CI, 0.7–7.0]), though no formal statistical tests were performed.

In summary, while lamotrigine is not FDA approved for the treatment of acute bipolar I or II depression, the above data suggest a role in more severely depressed symptoms.

Bipolar disorder: maintenance. Lamotrigine is currently FDA approved for the maintenance treatment of bipolar I disorder, though recent Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders collaborative updated guidelines remind prescribers of its limited ability to prevent mania.[24] Evidence specific for the use of lamotrigine in bipolar II disorder has led to its recommendation as a second-line maintenance therapy.[24] Although subjects with bipolar II disorder have been included in other trials, this CANMAT recommendation is largely based on 2 retrospective, naturalistic studies in subjects with bipolar II disorder (total n = 61) taking lamotrigine augmentation for an average of 20 months who noted clinical improvement on this medication.[25,26]

Two 18-month, multicenter registration trials[2,3] examined the efficacy of lamotrigine in maintenance treatment for bipolar I disorder. Both were double-blind, parallel-group, randomized, placebo-controlled trials of lamotrigine and lithium maintenance treatment in bipolar I disorder, with one enrolling subjects who were recently depressed[2] and the other enrolling those who were recently manic or hypomanic.[3] These were both enriched studies with an open-label phase of lamotrigine titration, followed by randomization to lamotrigine or lithium for up to 18 months. In the first trial (n = 463), lamotrigine and lithium were each statistically superior to placebo in time to intervention for any mood episode (time to intervention: placebo, 93 days [95% CI, 58 to 180]; lithium, 170 days [95% CI, 105 to not calculable]; and lamotrigine 200 days [95% CI, 146 to 399]). Lamotrigine was significantly better at prolonging time to intervention for a depressive episode ($P = .047$), while lithium (but not lamotrigine) was statistically superior to placebo in prolonging time to intervention for a hypomanic, manic, or mixed episode ($P = .026$). The second trial (n = 175) had similar results, with lamotrigine and lithium each statistically superior to placebo in time to intervention for any mood episode (time to intervention: placebo, 85 days [95% CI, 37 to 121]; lithium, 292 days [95% CI, 123 to not calculable]; lamotrigine, 141 days [95% CI, 71 to not calculable]). Lamotrigine was superior to placebo at prolonging time to a depressive episode ($P = .02$), and lithium, but not lamotrigine, was superior to placebo at prolonging time to a manic, hypomanic, or mixed episode (lithium vs placebo, $P = .006$; lamotrigine vs placebo, $P = .28$).

A pooled analysis[27] of these 2 trials,[2,3] demonstrated significantly increased time to intervention for a mood episode in lamotrigine versus placebo ($P < .001$) as well as lithium versus placebo ($P < .001$), with no statistical difference between lamotrigine and lithium monotherapy. Lamotrigine, but not lithium, was statistically superior to placebo at prolonging time to intervention for a depressive episode (lamotrigine, $P = .009$; lithium, $P = .120$). Notably, both lamotrigine and lithium were statistically superior to placebo at prolonging the time to intervention for a manic, hypomanic, or mixed episode (median survival: placebo, 86 days [95% CI, 58 to 121]; lithium, 184 days [95% CI, 119 to not calculable]; lamotrigine, 197 days [95% CI, 144 to 388]), though lithium was superior to lamotrigine ($P = .030$). However, with additional analyses adjusting for index mood, only lithium was shown to be significant for time to intervention for mania (lithium vs placebo, $P < .001$; lamotrigine vs placebo, $P = .149$; lithium vs lamotrigine, $P = .024$).

Licht et al[28] performed an open, randomized effectiveness study comparing lamotrigine and lithium for maintenance treatment in bipolar I disorder. Subjects from this nonenriched study were followed up to 5 years, with no differences noted between effectiveness of lithium and lamotrigine for preventing mood episodes, though lamotrigine was better tolerated.

Calabrese et al[29] performed a 26-week, double-blind, randomized, placebo-controlled trial in subjects with rapid cycling bipolar I and II disorders. Following an open stabilization phase of lamotrigine titration, responders were randomized to lamotrigine monotherapy versus placebo. In this negative trial, the 2 treatment groups did not differ by time to additional pharmacotherapy, the primary outcome measure. However, when subjects were categorized into bipolar I and II disorder, rapid-cycling subtypes, several secondary variables did demonstrate differences, but only for the bipolar II disorder subtype. These included lamotrigine's superiority to placebo on survival (subjects were terminated for any premature discontinuation) ($P = .015$) and lack of relapse after 6 months ($P = .04$).

Goldberg et al[30] utilized data from the self-reported prospective Life Chart Method (LCM) collected during the rapid-cycling study[29] to examine weekly mood shifts over a period of 26 weeks, comparing the number of subjects who achieved euthymia across weeks. They found that subjects taking lamotrigine were 1.8 times more likely than those taking placebo to achieve euthymia, as indicated on LCM, at least once weekly over 6 months (95% CI, 1.03–3.13, $P = .014$).

Risk of Switching Into Mania/Hypomania

In a secondary analysis[31] of the subjects with bipolar I disorder enrolled in the Calabrese et al[2] study, including those enrolled during the open-label, prerandomization phase, the lamotrigine group did not differ from placebo in time to emergence of mania during the first 6 months (hazard ratio = 0.79; 95% CI, 0.53–1.16). Also, in the previously described report[14] summarizing 5 RCTs in acute bipolar depression, the incidence of all mania (ie, mania, hypomania, mixed episodes) across studies was low and did not differ significantly between lamotrigine and placebo (3.8% and 3.3%, respectively).

Unipolar Depression

Monotherapy. Three unpublished double-blind, randomized, placebo-controlled trials with data discussed in a review by Amann et al[12] (SCA20022, SCA20025, SCAA2011) evaluated the efficacy of lamotrigine monotherapy in unipolar depression in a total of 750 subjects taking lamotrigine (≤ 200 mg/d) for up to 8 weeks. None demonstrated significant differences between groups in change in HDRS scores or in number of responders. Of note, the desipramine group also did not separate from placebo in the 1 study in which it was an active comparator. In summary, lamotrigine monotherapy has no demonstrated efficacy in unipolar depression.

Augmentation. A double-blind, randomized, placebo-controlled trial[32] investigated adjunctive lamotrigine added to paroxetine for acute unipolar depression in 40 subjects, though only 20 subjects were diagnosed with a recurrent major depressive episode (Table 2). Both the lamotrigine and placebo groups demonstrated a significant improvement in total HDRS score ($P < .0001$), with no significant differences between groups. However, when each of the 21 HDRS items was analyzed separately using analysis of variance, significant advantages were found with lamotrigine over placebo on depressed mood ($P = .0019$), guilt feelings ($P = .0011$), and work and interest ($P = .049$). Additionally, lamotrigine demonstrated significant efficacy versus placebo on the CGI-Severity of Illness scale ($P = .0205$). No differences were found in treatment effects between mildly and severely depressed subjects.

Barbosa et al[33] randomly assigned 23 subjects to either lamotrigine (≤ 100 mg/d) or placebo, in addition to a fixed dose of fluoxetine 20 mg/d, in a 6-week trial. Of note, the sample included subjects with bipolar II depression (n = 8) and with unipolar depressive disorder (n = 15). After 6 weeks, no significant differences were found between the 2 groups on HDRS or MADRS mean ± SD scores, though subjects taking lamotrigine had significantly improved CGI-Severity of Illness scores (lamotrigine, 2.15 ± 1.28; placebo, 3.40 ± 1.17; $P = .0308$) and CGI-Improvement scores (lamotrigine, 1.46 ± 0.66; placebo, 2.22 ± 0.83; $P = .0341$) compared to placebo.

In a multicenter, double-blind, randomized, placebo-controlled trial[34] of lamotrigine augmentation in treatment-refractory unipolar depression, defined as failure of at least 1 adequate trial of an antidepressant, subjects with scores ≥ 15 on HDRS (n = 96) following 8 weeks of open-label paroxetine were randomized to 10 weeks of augmentation with lamotrigine (100–400 mg/d) versus placebo. No significant difference in change in MADRS score was seen between lamotrigine augmentation and placebo. However, post hoc analysis of data from study end point noted a significantly higher response to lamotrigine compared to placebo in the more severely depressed and more treatment-resistant subjects.

In addition to these RCTs, lamotrigine and lithium were compared as adjunctive therapy for treatment-resistant unipolar depression in several open, observational, comparative studies[35–38] (total n = 204), with similar results between groups on most measures, including partial response, response, and remission in subjects with treatment-resistant depression. Subjects taking lithium demonstrated an earlier response in 1 study[35] though the lamotrigine group demonstrated better tolerability. In another,[38] a significant clinical improvement was noted within the second treatment week in the lamotrigine group compared to the lithium group ($P = .01$ vs lithium), but otherwise, results were comparable.

Several open-label lamotrigine augmentation studies[39–41] (total n = 51) demonstrated improvement in depressive symptoms, including a 25% decrease in HDRS scores after 1 month,[39] a superior response to combination with sertraline versus sertraline alone on the CGI scale,[40] and significant improvements compared to baseline on CGI-Severity of Illness, MADRS, and GAF scores, both at 8 weeks and 6 months.[41]

Three retrospective chart reviews[42–44] (total n = 96) found response rates on the CGI scale from 40.5%–76%[42,43] in addition to significant improvement on target symptoms, including depressed mood ($P < .001$), loss of interest ($P < .01$),

anxiety ($P < .001$), irritability ($P < .05$), (low) energy ($P < .01$), and cognitive impairment ($P < .001$).[44]

In summary, no current role exists for lamotrigine in the augmentation treatment of unipolar depression. However, augmentation trials for unipolar depression, although mostly open label and case series, suggest this may be an area for further study on a larger scale.

Borderline Personality Disorder

Two published double-blind, randomized, placebo-controlled trials of the use of lamotrigine in borderline personality disorder (total n = 55) have been conducted, ranging in duration from 8 to 12 weeks.[45–47] Data reported included significant improvements in anger initially and at 18-month follow-up observation,[45,46] as well as a significant decrease in affective instability and impulsivity at study end.[47] In 2 retrospective case reviews,[48,49] 11 of 13 subjects taking lamotrigine noted improvement in CGI scores over 3 months (from 5 or 6 to 1 or 2) and 3 of 8 demonstrated improvement in mean *DSM-IV* GAF score from 40s to 80s during 3–4 months, including absence of impulsive sexual, drug-taking, and suicidal behaviors. Preston et al[50] retrospectively examined data from 2 double-blind, randomized, placebo-controlled trials[2,3] of bipolar disorder subjects to investigate the comorbidity of borderline personality disorder, as well as the effect of lamotrigine on dimensions of borderline personality. With treatment, the average decrease of burden in borderline personality disorder symptoms in comorbid bipolar subjects was 45%. On the basis of these data, lamotrigine appears promising for symptoms of borderline personality disorder, including anger, impulsivity, and affective instability, but data to support its use are insufficient.

Schizophrenia

The inhibition of excessive glutamate release in the brain thought to occur with lamotrigine treatment has lead researchers to consider its use in schizophrenia because of the evidence suggesting dysfunctional glutamatergic neurotransmission in the pathophysiology of this disorder.[51] In an intervention review[52] of lamotrigine augmentation in schizophrenia with individual data extraction from 5 randomized, placebo-controlled trials (total n = 537), no differences were found between groups in global response (n = 208, 1 RCT; RR = 1.06, 95% CI, 0.73 to 1.54), but a significant reduction was found in the PANNS total scores (n = 67, 2 RCTs; weighted mean difference = −16.88; 95% CI, −8.57 to −25.18; $P = .0001$) as well as subscale scores of positive symptoms (n = 65, 2 RCTs; weighted mean difference = −5.10; 95% CI, −8.86 to −1.34) and negative symptoms (n = 65, 2 RCTs; weighted mean difference = −5.10; 95% CI, −8.86 to −1.34). The studies suggested no significant benefit from adjuvant lamotrigine on depressive symptoms in schizophrenia.

Several of these trials were included in a systematic review with meta-analysis[53] of lamotrigine in clozapine-resistant schizophrenia. Subjects enrolled in 5 double-blind, randomized, placebo-controlled trials ranging in duration from 10 to 24 weeks noted benefits of lamotrigine augmentation (100–400 mg/d) on primary outcome measures, including total PANSS score and total BPRS score, as well as on secondary measures including improvement in positive symptoms (standardized mean difference = 0.34; 95% CI, 0.02–0.65) and negative symptoms (standardized mean difference = 0.43; 95% CI, 0.11–0.76; $P = .008$). In the binary data analysis, lamotrigine augmentation was associated with a significantly higher response rate (defined by reduction of 20% or more in global score) than placebo (OR = 0.19; 95% CI, 0.09–0.43; $z = 3.97$; $P < .001$; NNT = 4; 95% CI, 3–6).

These data suggest a modest effect of lamotrigine, particularly in clozapine-resistant schizophrenia, for which treatment options are limited. However, these studies are relatively small, and the use of lamotrigine in schizophrenia does not currently have support.

Anxiety Disorders

Only 1 double-blind, randomized, placebo-controlled trial[54] of lamotrigine monotherapy (12 weeks at 500 mg/d) has been completed in subjects with PTSD. While the sample size was too small to measure a meaningful effect size, 5 of 10 subjects (50%) in the lamotrigine group responded as measured by changes in the Duke Global Rating for PTSD Scale compared to 1 of 4 (25%) in the placebo group. Additionally, improvement in reexperiencing and avoidance/numbing symptoms was seen in the lamotrigine group, with mean ± SD score changes of 0.7 ± 1.4 and 0.6 ± 1.6, respectively, while no changes were noted in the placebo group (0.0 ± 0.0 change for both).

Only single case reports and small case series[55–57] have evaluated the efficacy of lamotrigine in obsessive-compulsive disorder, with mixed results. Results demonstrated improvement in only 3 of 11 patients, though 1 with improvement had a concurrent increase in panic symptoms.[55–57] Only 1 case series[58] of lamotrigine (≤ 200 mg/d) as monotherapy or augmentation in panic disorder with agoraphobia has been published. Results in the augmentation group were mixed, but the patient taking lamotrigine monotherapy exhibited a significant improvement of anxiety symptoms with the dosage of 50 mg/d and complete cessation of panic attacks at 150 mg/d.

Safety/Tolerability

With the exception of rare serious rash, lamotrigine is fairly well tolerated, with a recent review[59] of 12 placebo-controlled trials of lamotrigine for acute and maintenance therapy demonstrating headache, nausea, and mild rash as the most common side effects. Overall, the adverse event profile of lamotrigine was comparable to that of placebo. Significant weight gain is rare.[17,18,59] Additionally, severe sedation and cognitive side effects appear to be relatively uncommon.[59] In comparison studies, the proportion of subjects withdrawn from the studies due to adverse events was higher in subjects taking lithium than those taking lamotrigine.[59] A trend for higher incidence rates of some adverse events was found among subjects with flexible dosing schedules (dose range:

400–500 mg/d) compared to adverse event rates with doses under 200 mg/d. However, data were insufficient to declare a clear association between adverse events and lamotrigine dose.[59]

Rash. Rash is considered a common side effect of lamotrigine in the treatment of epilepsy and mood disorders and occurs in 8%–10% of treated patients.[59–61] Maintenance treatment with lamotrigine demonstrated a lower incidence of any rash compared to short-term treatment (2.3% vs 9.1%).[59] Types of rashes include mild forms, such as simple morbilliform rash, urticaria, and erythema multiforme, and more severe skin reactions, such as hypersensitivity syndrome, Stevens-Johnson syndrome, and toxic epidermal necrolysis.[61] These more severe rashes, which are very rare, may involve fever, lymphadenopathy, elevated liver enzymes, nephritis, thrombocytopenia/leucopenia, pneumonitis, severe exanthematous rash, mucocutaneous blistering or crusting, and exfoliative dermatitis.[61] Toxic epidermal necrolysis is the most serious because of its greater likelihood of causing corneal and skin scarring and mortality at rates of approximately 25%–30%.[61] Examining pooled clinical trials of bipolar and other mood disorders, Seo et al[59] reported 1 serious rash in 1,233 subjects (0.08%) using lamotrigine for monotherapy, and 2 in 1,538 (0.13%) using it as adjunctive therapy. Fewer than 10 deaths were attributed to skin rash from lamotrigine from an estimated worldwide exposure of more than 950,000 subjects.[62] Across clinical trials using lamotrigine as adjunctive therapy in epilepsy, the risk of serious rash was highest in the first 6 weeks of treatment, occurring only occasionally up to 12 weeks of treatment and only rarely after that (incidence data not provided).[61] Concurrent use of valproic acid and rapid rate of lamotrigine titration can increase risk of serious rash.[59]

CONCLUSIONS

Lamotrigine is generally well tolerated, with headache, nausea, and mild rash occurring most commonly. Contrary to many psychotropic medications, it carries a relatively low rate of weight gain, metabolic changes, or cognitive effects and does not interact significantly with many psychotropic medications, with the exception of several anticonvulsants.

Support for the use of lamotrigine is most robust and has an FDA indication for the maintenance treatment of bipolar disorder, with particularly clear efficacy in prevention of depressive episodes. Data in acute bipolar depression are suggestive but not conclusive. Several individual trials have demonstrated limited effect, but meta-analyses suggest benefit, especially for more severely depressed subjects. Data are reassuring regarding switch rates with lamotrigine use, showing no increase risk for switch over placebo. This makes lamotrigine a reasonable choice for the treatment of acute bipolar depression in patients already on mood stabilizers, including those who have demonstrated adverse responses or side effects, such as switching, on commonly used antidepressants.

Evidence for efficacy of lamotrigine in unipolar depression is incomplete, although the double-blind, RCTs, which noted benefit on the CGI and subsets of symptoms, including mood and guilt, and improved response in more severely depressed subjects; multiple chart reviews; and open-label studies, including comparisons with lithium, were promising for its use. Additional randomized, placebo-controlled trials are required to further evaluate its efficacy in these patients.

Data are limited in borderline personality disorder, but appear promising on symptoms of anger, impulsivity, and affective instability. In schizophrenia, few studies have been done, though some data are suggestive of a positive effect on both negative and positive psychotic symptoms, particularly in clozapine-resistant subjects for whom treatments are few. Use of lamotrigine in anxiety disorders, including PTSD, obsessive-compulsive disorder, and panic disorder with agoraphobia, has not been well studied. To summarize, currently, data to support use of lamotrigine are lacking in borderline personality disorder, schizophrenia, and anxiety disorders.

Study Limitations

This review involves data found only via a search of PubMed, MEDLINE, and a hand search of relevant literature between 1990 and 2012 available in English language and, therefore, may have missed valuable unpublished data or other data unavailable under these search criteria.

Drug names: carbamazepine (Carbatrol, Equetro, and others), citalopram (Celexa and others), clozapine (Clozaril, FazaClo, and others), desipramine (Norpramin and others), fluoxetine (Prozac and others), gabapentin (Neurontin, Gralise, and others), lamotrigine (Lamictal and others), lithium (Lithobid and others), olanzapine-fluoxetine combination (Symbyax and others), paroxetine (Paxil, Pexeva, and others), phenytoin (Dilantin, Phenytek, and others), primidone (Mysoline and others), risperidone (Risperdal and others), sertraline (Zoloft and others), valproic acid (Stavzor, Depakene, and others).

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REFERENCES

1. Smith D, Baker G, Davies G, et al. Outcomes of add-on treatment with lamotrigine in partial epilepsy. *Epilepsia*. 1993;34(2):312–322.
2. Calabrese JR, Bowden CL, Sachs G, et al; Lamictal 605 Study Group. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. *J Clin Psychiatry*. 2003;64(9):1013–1024.
3. Bowden CL, Calabrese JR, Sachs G, et al; Lamictal 606 Study Group. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. *Arch Gen Psychiatry*. 2003;60(4):392–400.
4. Lamictal (lamotrigine) [package insert]. Research Triangle Park, NC: GlaxoSmithKline 2011.

5. Thomas SP, Nandhra HS, Jayaraman A. Systematic review of lamotrigine augmentation of treatment resistant unipolar depression (TRD). *J Ment Health*. 2010;19(2):168–175.
6. Perucca E. Clinical pharmacology and therapeutic use of the new antiepileptic drugs. *Fundam Clin Pharmacol*. 2001;15(6):405–417.
7. Gaffield ME, Culwell KR, Lee CR. The use of hormonal contraception among women taking anticonvulsant therapy. *Contraception*. 2011;83(1):16–29.
8. Ohman I, Vitols S, Tomson T. Lamotrigine in pregnancy: pharmacokinetics during delivery, in the neonate, and during lactation. *Epilepsia*. 2000;41(6): 709–713.
9. Kaufman KR, Gerner R. Lamotrigine toxicity secondary to sertraline. *Seizure*. 1998;7(2):163–165.
10. Pisani F, Oteri G, Russo MF, et al. The efficacy of valproate-lamotrigine comedication in refractory complex partial seizures: evidence for a pharmacodynamic interaction. *Epilepsia*. 1999;40(8):1141–1146.
11. Besag FMC, Berry DJ, Pool F, et al. Carbamazepine toxicity with lamotrigine: pharmacokinetic or pharmacodynamic interaction? *Epilepsia*. 1998;39(2): 183–187.
12. Amann B, Born C, Crespo JM, et al. Lamotrigine: when and where does it act in affective disorders? a systematic review. *J Psychopharmacol*. 2011;25(10): 1289–1294.
13. Calabrese JR, Bowden CL, Sachs GS, et al. A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. Lamictal 602 Study Group. *J Clin Psychiatry*. 1999;60(2):79–88.
14. Calabrese JR, Huffman RF, White RL, et al. Lamotrigine in the acute treatment of bipolar depression: results of five double-blind, placebo-controlled clinical trials. *Bipolar Disord*. 2008;10(2):323–333.
15. Geddes JR, Calabrese JR, Goodwin GM. Lamotrigine for treatment of bipolar depression: independent meta-analysis and meta-regression of individual patient data from five randomised trials. *Br J Psychiatry*. 2009;194(1):4–9.
16. Frye MA, Ketter TA, Kimbrell TA, et al. A placebo-controlled study of lamotrigine and gabapentin monotherapy in refractory mood disorders. *J Clin Psychopharmacol*. 2000;20(6):607–614.
17. Brown EB, McElroy SL, Keck PE Jr, et al. A 7-week, randomized, double-blind trial of olanzapine/fluoxetine combination versus lamotrigine in the treatment of bipolar I depression. *J Clin Psychiatry*. 2006;67(7):1025–1033.
18. Brown E, Dunner DL, McElroy SL, et al. Olanzapine/fluoxetine combination vs lamotrigine in the 6-month treatment of bipolar I depression. *Int J Neuropsychopharmacol*. 2009;12(6):773–782.
19. Schaffer A, Zuker P, Levitt A. Randomized, double-blind pilot trial comparing lamotrigine versus citalopram for the treatment of bipolar depression. *J Affect Disord*. 2006;96(1–2):95–99.
20. Nierenberg AA, Ostacher MJ, Calabrese JR, et al. Treatment-resistant bipolar depression: a STEP-BD equipoise randomized effectiveness trial of antidepressant augmentation with lamotrigine, inositol, or risperidone. *Am J Psychiatry*. 2006;163(2):210–216.
21. van der Loos ML, Mulder PG, Hartong EG, et al; LamLit Study Group. Efficacy and safety of lamotrigine as add-on treatment to lithium in bipolar depression: a multicenter, double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2009;70(2):223–231.
22. van der Loos ML, Mulder P, Hartong EG, et al; LamLit Study Group. Efficacy and safety of two treatment algorithms in bipolar depression consisting of a combination of lithium, lamotrigine or placebo and paroxetine. *Acta Psychiatr Scand*. 2010;122(3):246–254.
23. van der Loos ML, Mulder PG, Hartong EG, et al; LamLit Study Group. Long-term outcome of bipolar depressed patients receiving lamotrigine as add-on to lithium with the possibility of the addition of paroxetine in nonresponders: a randomized, placebo-controlled trial with a novel design. *Bipolar Disord*. 2011;13(1):111–117.
24. Yatham LN, Kennedy SH, Schaffer A, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2009. *Bipolar Disord*. 2009;11(3):225–255.
25. Sharma V, Khan M, Corpse C. Role of lamotrigine in the management of treatment-resistant bipolar II depression: a chart review. *J Affect Disord*. 2008;111(1):100–105.
26. Jung I, Lee M, Kang B, et al. Lamotrigine treatment for patients with bipolar II disorder: retrospective report of 30 cases. *Bipolar Disord*. 2008;10(suppl 1): 45–46.
27. Goodwin GM, Bowden CL, Calabrese JR, et al. A pooled analysis of 2 placebo-controlled 18-month trials of lamotrigine and lithium maintenance in bipolar I disorder. *J Clin Psychiatry*. 2004;65(3):432–441.
28. Licht RW, Nielsen JN, Gram LF, et al. Lamotrigine versus lithium as maintenance treatment in bipolar I disorder: an open, randomized effectiveness study mimicking clinical practice: The 6th trial of the Danish University Antidepressant Group (DUAG-6). *Bipolar Disord*. 2010;12(5): 483–493.
29. Calabrese JR, Suppes T, Bowden CL, et al. A double-blind, placebo-controlled, prophylaxis study of lamotrigine in rapid-cycling bipolar disorder. Lamictal 614 Study Group. *J Clin Psychiatry*. 2000;61(11):841–850.
30. Goldberg JF, Bowden CL, Calabrese JR, et al. Six-month prospective life charting of mood symptoms with lamotrigine monotherapy versus placebo in rapid cycling bipolar disorder. *Biol Psychiatry*. 2008;63(1):125–130.
31. Goldberg JF, Calabrese JR, Saville BR, et al. Mood stabilization and destabilization during acute and continuation phase treatment for bipolar I disorder with lamotrigine or placebo. *J Clin Psychiatry*. 2009;70(9): 1273–1280.
32. Normann C, Hummel B, Schärer LO, et al. Lamotrigine as adjunct to paroxetine in acute depression: a placebo-controlled, double-blind study. *J Clin Psychiatry*. 2002;63(4):337–344.
33. Barbosa L, Berk M, Vorster M. A double-blind, randomized, placebo-controlled trial of augmentation with lamotrigine or placebo in patients concomitantly treated with fluoxetine for resistant major depressive episodes. *J Clin Psychiatry*. 2003;64(4):403–407.
34. Barbee JG, Thompson TR, Jamhour NJ, et al. A double-blind placebo-controlled trial of lamotrigine as an antidepressant augmentation agent in treatment-refractory unipolar depression. *J Clin Psychiatry*. 2011;72(10): 1405–1412.
35. Schindler F, Anghelescu I. The LILA-Study: an observational study comparing the efficacy of lithium vs lamotrigine as an augmentation strategy for treatment-resistant depression (TRD). Abstract 140. Proceedings from the 59th Annual Meeting of the Society of the Society of Biological Psychiatry (SOBP). New York, NY; April 29–May 1, 2004.
36. Schindler F, Anghelescu IG. Lithium versus lamotrigine augmentation in treatment resistant unipolar depression: a randomized, open-label study. *Int Clin Psychopharmacol*. 2007;22(3):179–182.
37. Rybakowski J, Tuszewska M. Lithium or lamotrigine augmentation in treatment-resistant depression. *Int Clin Psychopharmacol*. 2006;9(suppl 1);s232.
38. Ivković M, Damjanović A, Jovanović A, et al. Lamotrigine versus lithium augmentation of antidepressant therapy in treatment-resistant depression: efficacy and tolerability. *Psychiatr Danub*. 2009;21(2):187–193.
39. Baloescu A, Grigorescu G, Gheorghe MD. LTG in the treatment of resistant depression. Abstract 93. 14th Association of European Psychiatrists Congress; March 4–8, 2006; Nice, France.
40. Dimellis D, Kouniakis F. Lamotrigine as an adjunctive agent for treatment resistant depressed patients already treated with sertraline–an open-label study. *Int J Neuropsychopharmacol*. 2004;2:S162.
41. Gabriel A. Lamotrigine adjunctive treatment in resistant unipolar depression: an open, descriptive study. *Depress Anxiety*. 2006;23(8):485–488.
42. Barbee JG, Jamhour NJ. Lamotrigine as an augmentation agent in treatment-resistant depression. *J Clin Psychiatry*. 2002;63(8):737–741.
43. Rocha FL, Hara C. Lamotrigine augmentation in unipolar depression. *Int Clin Psychopharmacol*. 2003;18(2):97–99.
44. Gutierrez RL, McKercher RM, Galea J, et al. Lamotrigine augmentation strategy for patients with treatment-resistant depression. *CNS Spectr*. 2005; 10(10):800–805.
45. Tritt K, Nickel C, Lahmann C, et al. Lamotrigine treatment of aggression in female borderline-patients: a randomized, double-blind, placebo-controlled study. *J Psychopharmacol*. 2005;19(3):287–291.
46. Leiberich P, Nickel MK, Tritt K, et al. Lamotrigine treatment of aggression in female borderline patients, pt 2: an 18-month follow-up. *J Psychopharmacol*. 2008;22(7):805–808.
47. Reich DB, Zanarini MC, Bieri KA. A preliminary study of lamotrigine in the treatment of affective instability in borderline personality disorder. *Int Clin Psychopharmacol*. 2009;24(5):270–275.
48. Weinstein W, Jamison KL. Retrospective case review of lamotrigine use for affective instability of borderline personality disorder. *CNS Spectr*. 2007; 12(3):207–210.
49. Pinto OC, Akiskal HS. Lamotrigine as a promising approach to borderline personality: an open case series without concurrent *DSM-IV* major mood disorder. *J Affect Disord*. 1998;51(3):333–343.
50. Preston GA, Marchant BK, Reimherr FW, et al. Borderline personality disorder in patients with bipolar disorder and response to lamotrigine. *J Affect Disord*. 2004;79(1–3):297–303.
51. Goff DC, Coyle JT. The emerging role of glutamate in the pathophysiology and treatment of schizophrenia. *Am J Psychiatry*. 2001;158(9):1367–1377.
52. Premkumar TS, Pick J. Lamotrigine for schizophrenia. *Cochrane Database Syst Rev*. 2006;18(4):CD005962.
53. Tiihonen J, Wahlbeck K, Kiviniemi V. The efficacy of lamotrigine in clozapine-resistant schizophrenia: a systematic review and meta-analysis.

Schizophr Res. 2009;109(1–3):10–14.
54. Hertzberg MA, Butterfield MI, Feldman ME, et al. A preliminary study of lamotrigine for the treatment of posttraumatic stress disorder. *Biol Psychiatry*. 1999;45(9):1226–1229.
55. Kumar TC, Khanna S. Lamotrigine augmentation of serotonin re-uptake inhibitors in obsessive-compulsive disorder. *Aust N Z J Psychiatry*. 2000;34(3):527–528.
56. Uzun Ö. Lamotrigine as an augmentation agent in treatment-resistant obsessive-compulsive disorder: a case report. *J Psychopharmacol*. 2010;24(3):425–427.
57. Bisol LW, Lara DR. Improvement of obsessive-compulsive disorder with divalproex and lamotrigine in two patients with bipolar II disorder. *Pharmacopsychiatry*. 2009;42(1):37–39.
58. Masdrakis VG, Papadimitriou GN, Oulis P. Lamotrigine administration in panic disorder with agoraphobia. *Clin Neuropharmacol*. 2010;33(3):126–128.
59. Seo HJ, Chiesa A, Lee SJ, et al. Safety and tolerability of lamotrigine: results from 12 placebo-controlled clinical trials and clinical implications. *Clin Neuropharmacol*. 2011;34(1):39–47.
60. Calabrese JR, Sullivan JR, Bowden CL, et al. Rash in multicenter trials of lamotrigine in mood disorders: clinical relevance and management. *J Clin Psychiatry*. 2002;63(11):1012–1019.
61. Guberman AH, Besag FM, Brodie MJ, et al. Lamotrigine-associated rash: risk/benefit considerations in adults and children. *Epilepsia*. 1999;40(7):985–991.
62. Lamictal Advisory Board Briefing Document. Glaxo-Wellcome; 1997.