The Current Understanding of Lamotrigine as a Mood Stabilizer

Chang-Gyu Hahn, M.D., Ph.D.; Laszlo Gyulai, M.D.; Claudia F. Baldassano, M.D.; and Robert H. Lenox, M.D.

Objective: To examine whether lamotrigine has a unique role in the treatment of bipolar disorder, we evaluated the results of recent clinical trials and molecular and cell biological studies on lamotrigine.

Data Sources: Using keywords such as *bipolar disorder*, *lamotrigine*, *clinical trial*, *outcomes studies*, and *mechanisms*, we conducted a search for English-language articles on MEDLINE and Index Medicus and also on abstracts presented in recent research conferences.

Data Synthesis: Several studies have strongly suggested that lamotrigine is effective for the acute treatment of bipolar depression as well as for long-term maintenance treatment of bipolar disorder. Stevens-Johnson syndrome is a concern, but the incidence of this side effect may not be as high as previously believed, if dosing is slowly titrated. The action mechanisms underlying the mood-stabilizing effects of lamotrigine are unknown at present but recent studies have produced interesting leads. Lamotrigine modulates various ion channels, altering neuronal excitability. The use-dependent inhibition of neuronal firing by lamotrigine is potentially important because it could result in attenuating supranormal neuronal activities that are possibly associated with bipolar disorder. Lamotrigine inhibits the release of glutamate, similarly to lithium, and its possible association with mood-stabilizing or antidepressant effects needs to be further examined. Unlike lithium or valproic acid, however, lamotrigine does not down-regulate the expression of protein kinase C or MARCKS, suggesting that lamotrigine employs different intracellular mechanisms for long-term changes in neurobiology from those of lithium or valproic acid.

Conclusion: The efficacy of lamotrigine for bipolar depression may provide us with new options in the treatment of bipolar disorder. Examining the effects of lamotrigine on various molecular mechanisms in correlation with its unique efficacy on bipolar depression may enhance our understanding of action mechanisms of the mood stabilizers.

(J Clin Psychiatry 2004;65:791–804)

Received Feb. 14, 2003; accepted Sept. 29, 2003. From the Department of Psychiatry, University of Pennsylvania Medical Center, Philadelphia.

This work was supported by grant MH61912-01 from the National Institutes of Health, Bethesda, Md.; an award from the National Alliance for Research on Schizophrenia and Depression (NARSAD), Great Neck, N.Y. (Dr. Hahn); the Rooney and Kind Bipolar Research Fund (Dr. Gyulai); and an unrestricted grant from GlaxoSmithKline, Philadelphia, Pa.

Dr. Gyulai serves as a consultant to GlaxoSmithKline, Bristol-Myers, Abbott, and Novartis and has received grant/research support and honoraria from or serves on the speakers or advisory boards for GlaxoSmithKline, Abbott, Bristol-Myers, AstraZeneca, and Eli Lilly. Dr. Baldassano has received grant/research support from Elan Pharmaceutical and serves on the speakers or advisory boards for GlaxoSmithKline and AstraZeneca. Dr. Lenox is an employee of Aventis Pharmaceutical.

The authors thank Beatrice Mendez, B.A., Hilary Selby Polk, M.A., and Karen Oberheim, B.A., for editorial assistance.

Corresponding author and reprints: Chang-Gyu Hahn, M.D., Ph.D., Department of Psychiatry, University of Pennsylvania, 527 Clinical Research Building, 415 Curie Boulevard, Philadelphia, PA 19104 (e-mail: hahnc@mail.med.upenn.edu).

Bipolar illness is a severe and chronic mood disorder characterized by recurrent episodes of mania and depression.[1] While the current pathophysiologic understanding of the illness is far from complete, several agents have been successfully used for the treatment of the acute phases of the illness as well as for long-term prophylaxis. Lithium was the sole mood stabilizer for many years and has been extensively studied for its action mechanisms.[2] Over the last decade, several anticonvulsants have been introduced for the treatment of bipolar disorder. A number of groups have reported that a newer anticonvulsant, lamotrigine, in addition to its antiepileptic effect, may have a unique role in the treatment of bipolar disorder. Subsequent to the observation that quality of life and mood were much improved in epileptic patients after lamotrigine treatment,[3] the therapeutic effect of lamotrigine has been described in depressive episodes and maintenance phase of bipolar disorder as well as in rapid-cycling bipolar disorder (for previous reviews, see references 4–8). While lamotrigine appears to have a broad-spectrum efficacy in the management of bipolar disorder, recent evidence suggests that lamotrigine has efficacy in depressive phases of bipolar disorder. The U.S. Food and Drug Administration (FDA) recently approved lamotrigine for maintenance treatment of bipolar disorder.

In this review, we will assess the current understanding of lamotrigine as a mood stabilizer in bipolar disorder and

Table 1. Open-Label Studies of Lamotrigine in Bipolar Disorder

Study (N)	Diagnosis (% of total)	Study Design	Duration	Concomitant Medications	Outcome Measure	Results
Calabrese et al[10] (N = 1)	Bipolar I rapid-cycling	Case report, prospective	11 mo	None	HAM-D, MRS, GAS	Remission, decrease in HAM-D score, increase in GAS score
Walden et al[11] (N = 1)	Bipolar I manic	Case report, prospective	> 1 y	Valproate	CGI	Considerable improvement
Fogelson and Sternbach[12] (N = 7)	Bipolar I non–rapid-cycling (29%), rapid-cycling schizoaffective (14%)	Case series, prospective	8–65 wk	Lithium, carbamazepine, valproate, acetazolamide, atypical antipsychotics, dextroamphetamine, trazodone	4-Point clinical scale	4/7 Patients improved
Kusumakar and Yatham[13] (N = 6)	Bipolar rapid-cycling	Case series, prospective	> 3 wk	None	Clinical impression	4/6 Patients in remission
Kusumakar and Yatham[14] (N = 22)	Bipolar depressed non–rapid-cycling (77%), rapid-cycling (23%)	Prospective, add-on	6 wk	Valproate	≥ 50% Decrease in HAM-D score	16/22 Patients responded
Sporn and Sachs[15] (N = 16)	Bipolar I (81%), bipolar II (19%), depressed (56%), mixed (38%), manic (6%)	Case series, retrospective chart review	2–6 wk	Lithium, carbamazepine, atypical antipsychotics, antipsychotics, choline, antidepressants, thyroxine, benzodiazepines	CGI (response: CGI score = 2)	8/16 Patients responded
Fatemi et al[16] (N = 5)	Rapid-cycling bipolar I (20%), bipolar II (80%), depressed (80%), mixed (20%)	Case series, prospective	225 ± 28 d	Thyroid (N = 1); thyroid, lithium, divalproex (N = 1); none (N = 2)	BDI, YMRS, GAS	Improved on BDI, GAS (all patients were depressed at baseline)
Kotler and Matar[17] (N = 2)	Bipolar I, schizoaffective	Case reports	4–6 mo	Lithium, antidepressants, antipsychotics	Clinical impression	Both patients in full remission
Bowden et al,[18] Calabrese et al[19] (N = 75)	Bipolar I (83%); bipolar II(15 %); non–rapid-cycling (45%); rapid-cycling (55%); depressed (55%); manic, hypomanic, or mixed (41%)	Open, parallel-group, multicenter, prospective	48 wk	None: 38% (rapid-cycling: 32%, non–rapid-cycling: 6%) Otherwise: lithium, carbamazepine, valproate, benzodiazepines, antidepressants, atypical antipsychotics	MRS, HAM-D, GAS, CGI (response: ≥ 26%–50% decrease in MRS, HAM-D scores from baseline)	68% of depressed patients improved on HAM-D; 84% of manic/ hypomanic/mixed patients improved on MRS
Suppes et al[20] (N = 17)	Bipolar I (53%); bipolar II (47%); rapid-cycling (53%); depressed (65%); manic, hypomanic, and "mood labile" (35%)	Open case series, retrospective chart review, multicenter	159 ± 109 d	None: 12%; others: lithium, valproate, gabapentin, antipsychotics, antidepressants, benzodiazepines, thyroxine	CGI-BP change score (response: much or very much improved)	65% of patients improved
Walden et al[21] (N = 14)	Bipolar I rapid-cycling, manic	Open, prospective, randomized (lamotrigine vs lithium)	12 mo	Benzodiazepines	Relapse by clinical determination, HAM-D, YMRS	Lamotrigine: 43% without episodes; lithium: 0% without relapse

Abbreviations: BDI = Beck Depression Inventory, CGI = Clinical Global Impressions scale, CGI-BP = CGI for Bipolar Disorder, GAS = Global Assessment Scale, HAM-D = Hamilton Rating Scale for Depression, MRS = Manic Rating Scale, YMRS = Young Mania Rating Scale.

review the data from clinical trials on the therapeutic effects of lamotrigine in various phases of bipolar disorder. Recent studies on mechanisms of action of lamotrigine will also be reviewed. In the absence of a proper animal model of bipolar disorder, an understanding of the action mechanisms of lamotrigine in comparison with those of other mood stabilizers may contribute to an understanding of the pathophysiology of bipolar disorder. In addition, pharmacokinetics and adverse effects of lamotrigine will be reviewed.

DATA SOURCES

We reviewed the literature on the efficacy of lamotrigine for bipolar disorder as well as the literature on the studies of the action mechanisms of lamotrigine. Using keywords such as *bipolar disorder*, *lamotrigine*, *clinical trial*, *outcomes studies*, and *mechanisms*, we conducted a search for English-language articles on MEDLINE and Index Medicus and also on abstracts presented in recent research conferences.

CLINICAL STUDIES IN BIPOLAR DISORDER

Open-Label Studies

Since the case series of Weisler et al.[9] in 1994, there have been more than 20 open-label, uncontrolled case reports or studies examining lamotrigine in more than 250 patients with bipolar disorder.[10–27] Table 1 summarizes some of these studies. Patient populations studied were

quite heterogeneous, including bipolar I and bipolar II patients; patients in depressed, hypomanic, and mixed states; and patients with treatment-refractory and rapid-cycling forms of the disease. Clinical rating scales used in these studies ranged from standard bipolar mood rating scales[10,18,19,21] or the Clinical Global Impressions scales (CGI)[11,15,18–20] to clinical judgment.[13,17,21] Some were longitudinal, prospective studies,[18,19,21] whereas others were retrospective.[20] In some studies, lamotrigine was used as monotherapy[10,13]; in others, lamotrigine was used as an "add-on" medication.[14,15,18,19]

Two prospective, open-label studies strengthened the initial impression that lamotrigine has the potential to be an effective mood stabilizer.[18,19,21] The largest open study of lamotrigine in the treatment of bipolar patients to date found moderate-to-marked responses in 68% of depressed patients and 84% of patients entering in hypomanic, manic, or mixed states.[18,19] In this study, rapid-cycling patients showed less improvement in manic symptoms than did non–rapid-cycling patients; a subset of rapid-cycling patients with high baseline severity of manic symptoms experienced "little or no improvement" with lamotrigine, but both groups had equal improvement in depressive symptoms.[18] Lamotrigine's apparent efficacy in bipolar depression was a particularly important observation because treating bipolar depression is often a challenge for practicing physicians.[28] Walden et al.[21] described that lamotrigine reduced the number of affective relapses more than did lithium over a 12-month period in patients with rapid-cycling bipolar I disorder. The small number of subjects (total N = 14) clearly is a limiting factor in interpreting the results of the study.

These open studies suggested that lamotrigine had therapeutic effects in depressed, (hypo)manic, and mixed bipolar patients, with equivocal antimanic efficacy in rapid-cycling bipolar patients. However, given the varying methodology and study populations and the lack of a placebo arm, further investigation with double-blind, placebo-controlled trial designs was required.

Controlled Studies

Acute efficacy. Calabrese et al.[29] investigated the efficacy of lamotrigine for treating acute bipolar depression in a seminal, multicenter, double-blind, placebo-controlled, parallel-group study (Table 2[29–37]). Either lamotrigine monotherapy (50 or 200 mg/day) or placebo was administered to 195 depressed outpatients with bipolar I disorder without rapid-cycling course for at least 7 weeks. On the observed scores of the 17-item Hamilton Rating Scale for Depression (HAM-D-17), lamotrigine (50 mg/day and 200 mg/day) demonstrated antidepressant efficacy. No statistically significant difference was found, however, between the lamotrigine and placebo groups when last-observation-carried-forward (LOCF) analysis was used.

Lamotrigine (200 mg/day) showed significant antidepressant efficacy as measured by the Montgomery-Asberg Depression Rating Scale (MADRS)[38] in the observed and LOCF analyses compared with placebo, and in the responder analysis (54% vs. 29% for lamotrigine and placebo, respectively).[29] Both CGI-Severity of Illness scale (CGI-S) and CGI-Improvement scale (CGI-I) scores confirmed improved condition of the patients. Antidepressant response, as measured by the MADRS, was also significant in the group receiving a maximum of 50 mg/day of lamotrigine compared with the group receiving placebo (48% vs. 29 %, respectively).

Further analysis of this study[29] shows that, compared with placebo, lamotrigine at both doses significantly reduced "reported sadness" and "inability to feel," and lamotrigine 200 mg/day significantly reduced "lassitude," "inner tension," and "suicidal thoughts."[6] Lamotrigine's efficacy in treating the somatic symptoms of depression ("reduced sleep" and "reduced appetite") was less pronounced.[6,29] Antidepressant effect was observable (using the MADRS) after 3 weeks of treatment, at which time lamotrigine doses had been titrated to 50 mg/day in both the 50-mg/day and the 200-mg/day treatment groups. Thus, the time to onset of the antidepressant effect of lamotrigine and antidepressants appears to be comparable. Manic, hypomanic, or mixed episodes were reported as adverse events in 3% of patients receiving lamotrigine 50 mg/day, 8% of patients receiving lamotrigine 200 mg/day, and 5% of patients receiving placebo. Headache was the only adverse event that was more frequent in the lamotrigine groups than in the placebo group. The occurrence of rash was 14% and 11% in the 50-mg/day and 200-mg/day groups, respectively. These percentages were not significantly different from the occurrence of rash in the placebo group (11%); none of the rashes were serious. The authors concluded that lamotrigine possesses "significant antidepressant efficacy" in bipolar depression based on several measures of depression, although the results of the primary outcome measure (HAM-D-17) were equivocal. Future studies assessing the efficacy of lamotrigine in depression associated with rapid-cycling or type II bipolar disorder are required to further elucidate the acute antidepressant effects of lamotrigine in bipolar disorder.

Lamotrigine's efficacy in acute mania was studied in a 4-week, double-blind, parallel-group study.[32] Patients with bipolar I disorder who were currently manic were randomized to receive lamotrigine (N = 15, 100-mg/day final dose) or lithium (N = 15, 800-mg/day final dose). The mean Mania Rating Scale (MRS)[39,40] score improved significantly in all treatment groups compared with baseline. In addition, the time course of the decrease in MRS score is grossly consistent with that of the open-label, lamotrigine study in rapid-cycling bipolar disorder.[18] The interpretation of this study,[32] however, is somewhat lim-

Table 2. Randomized Double-Blind Studies of Lamotrigine in Bipolar Disorder

Study	Diagnosis (% of total)	Study Design	Duration	Concomitant Medications	Outcome Measure(s)	Results
Calabrese et al[29] (N = 195)	Bipolar I depressed outpatients	Multicenter, parallel-group, placebo-controlled	7 wk	Monotherapy lamotrigine 50 mg/d or 200 mg/d (sedative allowed in first 3 weeks)	HAM-D, MADRS, CGI-I, CGI-S	Decrease in MADRS: visitwise observed: lamotrigine > placebo in both lamotrigine groups; in LOCF: lamotrigine > placebo in 200-mg/d group only (also in CGI-I)
Frye et al[30] (N = 31)	Treatment-refractory bipolar I (36%), bipolar II (45%), unipolar (19%), rapid-cycling (92%) non–rapid-cycling (8%)	Single-center, placebo-controlled, crossover	6-wk phases	Monotherapy	CGI-BP (response: very much or much improved)	Response: lamotrigine, 52%; placebo, 23% in overall condition (p = .031)
Calabrese et al[31] (N = 182)	Outpatients rapid-cycling bipolar I (71%), bipolar II (29%), depressed (55%), manic/hypomanic (19%), mixed (7%), no episode (19%)	Multicenter, parallel-group, placebo-controlled (after open-label lamotrigine phase)	26 wk	Monotherapy	Time to additional pharmacotherapy, time to study discontinuation for any reasons, CGI-S, GAS	GAS score and time to discontinuation for any reasons: lamotrigine > placebo (in total sample and in bipolar II patients)
Ichim et al[32] (N = 30)	Hospitalized bipolar I, currently manic	Single-center, parallel-group (vs lithium)	4 wk	Monotherapy (except lorazepam prn)	MRS	MRS score decreased in all groups, lamotrigine = lithium
Calabrese et al,[33] Bowden et al[34] (N = 404 included in final analysis)	Bipolar I outpatients, most recently depressed	Multicenter, fixed-dose, parallel-groups (lamotrigine, lithium, placebo)	18 mo	Monotherapy	Time to medication intervention for affective episode, time to depressive episode, time to manic episode	Lamotrigine > placebo on time to intervention for affective episode, time to intervention for depressive episode; lithium > placebo on time to intervention for affective episode, time to intervention for manic episode
Bowden et al,[35,36] Calabrese et al[37] (N = 175)	Bipolar I outpatients, recently manic/ hypomanic	Multicenter, flexible-dose, parallel-groups (lamotrigine, lithium, placebo)	18 mo	Monotherapy	Time to medication intervention for affective episode, time to depressive episode, time to manic episode	Lamotrigine > placebo on time to intervention, time to depressive episode; lithium > placebo on time to intervention, time to manic episode

Abbreviations: CGI = Clinical Global Impressions scale, CGI-BP = CGI for Bipolar Disorder, CGI-I = CGI-Improvement, CGI-S = CGI Severity of Illness, GAS = Global Assessment Scale, HAM-D = Hamilton Rating Scale for Depression, LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale, MRS = Mania Rating Scale, YMRS = Young Mania Rating Scale.

ited by the small number of subjects, the relatively low serum lithium levels (0.743 mEq/L), and the short period of washout of other medications (1 day prior to randomization). On the other hand, 2 studies (as documented in a review by Calabrese et al.[4]) showed no efficacy of lamotrigine for the acute treatment of mania. A fair assessment of antimanic effects of lamotrigine for acute mania is difficult, however, because lamotrigine requires a slow titration.[4] In addition, clinicians often use concomitant antipsychotics or other mood stabilizers in the acute treatment of mania, which further reduces the naturalistic database on lamotrigine monotherapy in mania. Overall, the inconsistencies in the findings on the antimanic effects of lamotrigine do not support the agent as a preferred choice for the acute treatment of mania.

Maintenance efficacy. Recent double-blind, placebo-controlled maintenance studies give strong indication that lamotrigine is also effective in preventing affective relapses in both rapid-cycling and non–rapid-cycling bipolar disorder.[31,33–37,41–43]

Calabrese and colleagues[31] conducted a multicenter, double blind, placebo-controlled, parallel-group study of rapid-cycling bipolar patients using a flexible dose of lamotrigine (GSK 614 study). After an open-label phase, in which lamotrigine was added to 324 patients' current regimens to stabilize their condition (HAM-D score ≤ 14 and MRS score ≤ 12), 182 patients entered a 6-month, double blind, randomized phase, in which other medications were tapered and lamotrigine monotherapy (maximum dose = 500 mg/day) was compared with placebo. The primary outcome measure was the time to additional pharmacotherapy for emerging symptoms. Secondary efficacy measures included survival in study (time to withdrawal from the study for any reason), percentage of pa-

tients stable without relapse for 6 months, and changes in the Global Assessment Scale (GAS) and CGI-S scores.

On the primary outcome measure, the difference between lamotrigine and placebo did not reach statistical significance for the overall study population. However, when survival in study was evaluated, there was a significant difference favoring lamotrigine. Furthermore, 41% of patients who received lamotrigine, versus 26% of those who received placebo, were stable without relapse for 6 months. When the results of survival analyses were compared between the subtypes of bipolar disorder, no significant differences were seen between lamotrigine and placebo groups within bipolar I patients in terms of survival in study or time to additional pharmacotherapy. However, among bipolar II patients, survival in study was significantly increased in the lamotrigine treatment group compared with that in the placebo group. The maintenance efficacy of lamotrigine in rapid-cycling bipolar I disorder was poor in contrast to the acute antidepressant efficacy in non–rapid-cycling bipolar I disorder[29] or its maintenance efficacy in slow-cycling (4–6 episodes per year) or non–rapid-cycling bipolar I disorder.[33,34,36]

The poor maintenance efficacy of lamotrigine in rapid-cycling bipolar I disorders may be related to the high placebo response rate in bipolar I disorder that was observed in the Calabrese et al. (GSK 614) study,[31] although the reason for this high placebo-response group is unknown. Nevertheless, the number of patients with bipolar II disorder, constituting one third of the total randomized sample, makes the finding in bipolar II disorder robust.

Other positive predictors of efficacy in this study[31] were a higher number of previous affective episodes (≥ 6 episodes per year), male sex, onset after age 10 years, and no family history of depression but positive family history of bipolar disorder.[42,43] Lamotrigine was well tolerated, and no serious rashes occurred.

The authors concluded: "Lamotrigine monotherapy is a useful treatment for some patients with rapid-cycling bipolar disorder."[31(p841)] They acknowledged several methodological problems with this study, including possible selection bias that may have minimized the enrollment of more severely ill patients; this limitation may have resulted in an unexpectedly high placebo response rate within the bipolar I group. Finally, most of the relapses in the randomized, double-blind treatment phase were to a depressive episode; hence, the study provides weaker data pertaining to the maintenance efficacy of lamotrigine for mania than for depression.

The efficacy of lamotrigine in the maintenance treatment of bipolar disorder was further supported by 2 recently completed double-blind, placebo-controlled, multicenter studies.[33–37,41] One study[35–37] evaluated the efficacy of flexible-dose lamotrigine for the maintenance treatment of currently or recently manic patients. In the first phase of the study (GW 606),[35–37] 349 bipolar I patients with a current or recent manic or hypomanic episode received 8 to 16 weeks of open-label treatment, in which lamotrigine (100–200 mg/day) was added to current therapy or used as monotherapy.[35–37] This was followed by withdrawal of concomitant medications, and lamotrigine was given as monotherapy. Patients who were stabilized on lamotrigine monotherapy for at least 4 continuous weeks (CGI-S score ≤ 3) could enter the randomized phase. One hundred seventy-five patients were randomized to monotherapy with lamotrigine (100–400 mg/day), lithium (to achieve a serum lithium level of 0.8–1.1 mEq/L), or placebo for up to 18 months. The primary efficacy variable was time from randomization to "intervention for a mood episode." Lamotrigine and lithium were comparably effective, and both were superior to placebo in preventing recurrence of bipolar affective episodes. Time to treatment intervention for any mood episode was 141 days for lamotrigine, 292 days for lithium, and 85 days for placebo. Lamotrigine was superior to placebo in overall survival in study as well as time to intervention for a depressive episode but not time to intervention for a manic episode. Lithium was significantly superior to placebo in time to intervention for a manic but not a depressive episode. Lamotrigine was well tolerated during the 18-month treatment period.

Another controlled study (GW 605)[33,34] assessed the efficacy and tolerability of fixed doses of lamotrigine (50, 200, 400 mg) for maintenance treatment in currently or recently depressed bipolar I patients. The design was essentially the same as the aforementioned study (GW 606),[35–37] including the outcome measures, except that it had a fixed-dose design. A total of 958 patients were enrolled in the open-label lamotrigine treatment phase and 480 completed this phase. Four hundred sixty-three were randomized to lamotrigine, lithium, or placebo. Data for patients in the 50-mg lamotrigine arm were excluded from the final analysis. The final number of patients randomized to 200 or 400 mg of lamotrigine was 169. The primary efficacy analysis was conducted on 404 patients randomized to lamotrigine, 200 or 400 mg (N = 165); lithium (N = 120); or placebo (N = 119). Lamotrigine was superior to placebo in prolonging the time to treatment of the next mood episode but not when compared with lithium: the median time to treatment intervention for any affective episode was 200 days for lamotrigine, 93 days for placebo, and 170 days for lithium. Lamotrigine was superior to placebo in delaying time to intervention for depression but not compared with lithium. Lithium was effective in delaying intervention for manic episodes compared with either placebo or lamotrigine. Patients tolerated lamotrigine well: 9% of lamotrigine-treated patients and 10% of placebo-treated patients withdrew from the randomized phase of the study (NS). When the data from the 2 studies were combined, lamotrigine was clearly superior to placebo in preventing

depressive and, to a lesser degree, manic relapses, while lithium was effective in preventing manic/mixed relapses only.[41] It was concluded that lamotrigine is useful in long-term mood stabilization in patients with bipolar disorder.

In a double-blind, crossover trial,[30] the efficacies of lamotrigine, gabapentin, and placebo were compared in three 6-week periods in 31 patients with treatment-refractory affective disorders (81% bipolar). The primary outcome measure was the CGI for Bipolar Illness (CGI-BP)[44] supplemented by other standard rating instruments (HAM-D, Young Mania Rating Scale [YMRS]). The mean ± SD dose of lamotrigine was 274 ± 128 mg/day and of gabapentin was 3987 ± 856 mg/day. The overall response rate (CGI-BP score = very much or much improved) was 52% in the lamotrigine-treated patient group, with response in 44% of patients with mania and 45% of patients with depression. Overall response rates in the lamotrigine group were statistically higher than those in the placebo (23%) or gabapentin (26%) groups. Lamotrigine was more efficacious in decreasing the intensity of depression as measured by the HAM-D compared with gabapentin.

It needs to be further explored whether lamotrigine has differential maintenance efficacy for bipolar I and bipolar II disorders. In addition, bipolar disorder with psychotic features and bipolar disorder with comorbid psychiatric illnesses are other areas that require further studies.

Summary of Efficacy

Lamotrigine appears to have maintenance efficacy for overall bipolar morbidity. Evidence from controlled studies supports efficacy of lamotrigine in the acute treatment and relapse prevention of depressive episodes in bipolar disorder. The data on the efficacy of lamotrigine in mania, however, are either equivocal or limited for acute manic episodes as well as for manic symptoms during the maintenance phase. Lamotrigine appears to have therapeutic effects on rapid-cycling bipolar disorder, but its effects on type II rapid-cycling bipolar disorder were shown to be more pronounced than its effects on type I. While more controlled studies are clearly required, the foregoing evidence overall suggests that lamotrigine is a useful agent for bipolar disorder, for acute as well as long-term maintenance treatments.

LAMOTRIGINE MECHANISMS OF ACTION

Recent investigations of action mechanisms underlying the therapeutic effect of lithium and other mood stabilizers have been focused on signal transduction mechanisms, gene regulation, and modulation of ion channel activities. Many groups have investigated the effect of lamotrigine on the activities of various ion channels in comparison with other anticonvulsants. More recently, several groups have examined the effect of lamotrigine on neurotransmission and various signal transduction mechanisms. Because lamotrigine may have distinct effects on depressive symptoms of bipolar disorder, understanding its action mechanisms in comparison with other mood stabilizers may provide insight on how intracellular events are related to therapeutic effects of mood stabilizers on specific mood states.

High-Frequency Firing of Action Potentials

A number of groups have demonstrated that lamotrigine suppresses accelerated firing of action potentials in various paradigms,[45–47] whereas lamotrigine has little effect on normal physiologic properties of neuronal activity such as resting membrane potentials, low-frequency firing, and postsynaptic potentials. In a rat model of reverberatory seizures, as an example of accelerated firing, lamotrigine caused a dose-dependent decrease in the duration of the seizure discharge.[48] In contrast, under control conditions, lamotrigine does not alter neuronal excitability, paired-pulse inhibition, and long-term potentiation. Superfusion of rat hippocampal slices with magnesium-free media causes repetitive firing and synaptic epileptic activity. However, 50 μmol of lamotrigine, a therapeutically relevant concentration, was found to selectively inhibit afterdischarges in the epileptiform activity in the neurons.[47]

The effect of lamotrigine on repetitive firing and epileptiform activity may be mediated by the inhibition of glutamate release. The spontaneous bursting in hippocampal slices in the absence of magnesium can be blocked by a combination of alpha-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid (AMPA) and *N*-methyl-D-aspartate (NMDA) antagonists.[49,50] Lamotrigine was found to inhibit the release of glutamate evoked by veratridine, which acts to open voltage-gated Na^+ channels by preventing inactivation, but lamotrigine had no effects on basal glutamate release even at a much higher concentration, an observation that is consistent with the idea that lamotrigine inhibits overexcited neuronal activities without significant effects on basal states. If manic symptoms are associated with supranormal firing or increased excitatory neurotransmission, the observation that lamotrigine inhibits the rapid firing of action potentials and excessive glutamate release may suggest that the mood-stabilizing effect of lamotrigine is associated with its ability to normalize accelerated neurotransmission and signaling during the mood states of bipolar disorder.

Voltage-Gated Calcium Channels

Altered intracellular Ca^{2+} homeostasis has been implicated in the pathophysiology of bipolar disorder.[51,52] In platelets and neutrophils of manic patients, intracellular Ca^{2+} levels were found to be elevated, but they were "normalized" following lithium treatment.[53] Recent evidence suggests that lamotrigine alters intracellular Ca^{2+} homeo-

stasis by inhibiting specific channel subtypes in certain regions of the brain. In rat amygdala neurons, lamotrigine causes substantial inhibition of Ca^{2+} currents[54,55]; however, in the presence of the N-type Ca^{2+} channel blocker omega-conotoxin GVIA, the effect of lamotrigine on Ca^{2+} channels was prevented. This observation suggests that lamotrigine blocks N-type Ca^{2+} channels. While lamotrigine does not affect Ca^{2+} currents through T-type channels, there is evidence that lamotrigine inhibits mixed N- and P-type Ca^{2+} channels in some cell systems.[46] In studies with recombinant N-type Ca^{2+} channels expressed in the mammalian cell system, it was shown that the effect of lamotrigine is weakly voltage dependent.[56] Therefore, it appears that lamotrigine is not a broad-spectrum Ca^{2+} channel blocker, but rather inhibits specific subtypes of voltage-gated Ca^{2+} channels in specific regions of the brain.

The effects of mood-stabilizer treatment on intracellular Ca^{2+} homeostasis have been extensively studied, and it was shown that lithium treatment alters cytoplasmic intracellular Ca^{2+} in blood cells of bipolar patients.[52,53] It will be interesting to examine whether the effects of lamotrigine on voltage-gated Ca^{2+} channels are translated to changes in intracellular Ca^{2+} levels in blood cells of patients during treatment with lamotrigine.

Blockade of voltage-gated K^+ channels results in long-lasting enhancement of excitatory postsynaptic potentials (EPSPs) in amygdala slices. Recent studies have suggested that long-term changes in synaptic plasticity play a critically important role in mood stabilization. Interestingly, lamotrigine inhibits long-lasting enhancement of EPSPs caused by blockade of voltage-gated K^+ channels, suggesting that lamotrigine modifies synaptic plasticity, possibly via its effects on presynaptic and/or postsynaptic Ca^{2+} channels. Alternatively, lamotrigine may reduce glutamate release via presynaptic inhibition of Na^+ channels and subsequent reduction in action potential duration.

Voltage-Gated Sodium Channels

Whole-cell voltage clamp recordings in conjunction with recombinant ion channels have demonstrated that lamotrigine modulates Na^+ channel activity in various cell systems.[57–60] Neuronal action potentials require the proper opening and closing of voltage-gated Na^+ channels. As membrane potential reaches the threshold, Na^+ channels open briefly, resulting in the rising phase of action potentials. Subsequently, Na^+ channels are inactivated, and voltage-gated K^+ channels are activated, which together result in termination of action potentials. Na^+ channels recover quickly from inactivation and enter the resting state. Many groups have shown that lamotrigine inhibits Na^+ channel activity in a voltage-dependent manner. In various cell systems, when the membrane voltage was held at V_h –90 to –120 mV, at which virtually all channels are in resting state, the inhibitory effect of lamotrigine on Na^+ currents was minimal (IC_{50} of 500 to 1000 μmol).[57] However, when the membrane voltage was held at V_h –60 to –80 mV, lamotrigine produced substantial inhibition of Na^+ currents. The voltage dependence in lamotrigine's inhibitory effects on Na^+ channel activities has been demonstrated in rat hippocampal neurons and cerebellar granule neurons and in mouse neuroblastoma cells and others.[57–59] The inhibitory effect of lamotrigine on Na^+ currents also appears to be use- or frequency-dependent. In Chinese hamster ovary cells expressing Na^+ channels, lamotrigine produced a progressively increasing use-dependent inhibition when the cells were activated with longer pulses (20 ms), whereas lamotrigine did not cause significant inhibitory effects when the cells were stimulated with brief pulses.[47]

The voltage or use dependence of lamotrigine's inhibitory effects on Na^+ currents is thought to be related to its effects on slow inactivation state of Na^+ channels.[60] When neurons are hyperstimulated, as in seizures,[61] Na^+ channels enter a slow inactivation state, from which recovery is slower than recovery from normal stimulation. If bipolar disorder is associated with hyperstimulation of neurons in certain regions of the brain, the effects of lamotrigine on slow inactivation may in part explain its ability to normalize mood symptoms of the illness.

Neurotransmission

Regulation of neurotransmission in the brain's glutamate receptor system has been implicated in the antimanic effect of lithium. In an acute treatment paradigm, lithium has been shown to inhibit glutamate reuptake, which results in increased glutamate release.[62] In a chronic treatment paradigm, however, glutamate reuptake was found to be upregulated, which results in decreased glutamate release.[63] This chronic effect of lithium on the glutamate system has been interpreted to be associated with the antimanic properties of lithium treatment. Many groups have shown that lamotrigine inhibits the release of glutamate in various cell systems.[64–66] Lamotrigine was found to reduce glutamate release in synaptosomal preparations of cerebral cortex,[64] as well as in cortex in vivo using microdialysis.[65] Lamotrigine-induced glutamate inhibition also caused postsynaptic effects in a number of systems. In nerve terminals, the effect of lamotrigine on glutamate release is accompanied by reduction in depolarization-evoked increases in cytoplasmic Ca^{2+} concentration. In the entorhinal cortex, the effect of lamotrigine on glutamate release results in reduced frequency of spontaneous excitatory postsynaptic currents.[66]

A major inhibitory neurotransmitter in the brain, γ-aminobutyric acid (GABA), has been implicated for the action mechanisms of other mood stabilizers, such as valproic acid and topiramate; it is, therefore, of interest whether lamotrigine affects GABAergic neurotransmis-

sion. Several groups have examined the effects of lamotrigine in various regions of the central nervous system (CNS) and reported significant reductions of GABA release in rat spinal dorsal horn slices[67] and in rat cerebral cortical slices.[49,68] Interestingly, however, lamotrigine was found to increase both the amplitude and frequency of spontaneous $GABA_A$ receptor mediated postsynaptic current, suggesting an increased release of GABA.[66] More recently, in slice preparations from basolateral amygdala, it was demonstrated that lamotrigine decreased the frequency and amplitude of inhibitory postsynaptic potentials (IPSPs).[69] Given the conflicting results, further studies are clearly needed to establish the role of lamotrigine and ascertain the role of GABA in relation to the mood-stabilizing effects of lamotrigine.

Lamotrigine has been shown to have a neuroprotective effect in various paradigms of neurotoxicity such as hypothermia[70,71] and hypoxia.[72,73] It has been suggested that lamotrigine's inhibitory effect on glutamate release plays a role in its neuroprotective effect.[74,75] These observations are interesting, especially in light of recent studies that have demonstrated a neuroprotective effect of lithium in vitro,[76] in animal studies in vivo,[76–79] and in brain imaging of bipolar patients.[80] While the clinical consequences of lithium's neuroprotective effect in relation to its mood-stabilizing effect are unclear,[81] it will be important to elucidate the molecular mechanisms underlying the neuroprotective effects of lamotrigine in comparison with lithium.

Regulation of the serotonin (5-HT) system in depression and its association with the effects of antidepressants are well established. In human platelets and rat brain synaptosomes, lamotrigine was found to decrease 5-HT reuptake.[82] Carbamazepine, but not lithium or valproic acid, had a similar effect.[82] When $5\text{-}HT_{1A}$ receptor function was measured in platelets of healthy males with ipsapirone challenge (cortisol response and changes in temperature in response to single-dose oral ipsapirone), 1 week of lamotrigine treatment did not alter hypothermic or cortisol responses to ipsapirone.[83] Because lamotrigine might have efficacy in the depressive phases of bipolar disorder, it is of interest to examine regulation of neurotransmission by lamotrigine in 5-HT and other monoamine systems in the context of mood stabilization.

Signal Transduction Mechanisms

The role of signal transduction via adenylate cyclase, phosphoinositol hydrolysis, and the glycogen synthase kinase 3β system has been extensively studied in mood-stabilizer treatment.[2,84–86] While the therapeutic relevance of the findings of these studies remains to be elucidated, studies on animal brains, in vitro culture cells, peripheral blood cells, and postmortem human brains have supported the notion that some of these molecules are targeted in mood-stabilizer treatment.[84] Historically, lithium has been studied most extensively, and recent investigations have been expanded to valproic acid and other mood stabilizers. Thus, in order to investigate molecular mechanisms underlying the mood-stabilizing effect of lamotrigine, it will be important to determine whether the signal transduction mechanisms that are regulated by lithium or other mood stabilizers are also altered by lamotrigine. At present, the effects of lamotrigine on most of these intracellular signaling mechanisms are yet to be investigated.

Lithium is a noncompetitive inhibitor of inositol monophosphatase.[87–89] While lithium's effect on phosphoinositol signaling has been extensively studied,[90,91] lamotrigine's effect on phosphoinositol signaling has not been studied to date. It has been suggested that lithium attenuates coupling of G proteins to receptors and alters the expression of some isoforms of G proteins at the level of protein as well as messenger RNAs.[92–94] It will be interesting to examine whether lamotrigine also affects the activity of G protein and its expression. Lithium has been found to downregulate the activity of glycogen synthase kinase 3β,[95] and more recent evidence has shown that valproic acid has a similar effect.[96] The effects of lamotrigine on a number of other intracellular signaling components, such as adenylate cyclase and intracellular calcium, await examination.

Protein kinase C (PKC) plays a pivotal role in mediating long-term changes in neurons by initiating changes in neurotransmission via protein phosphorylation (e.g., nuclear proteins).[97] PKC and its substrate, myristoylated alanine-rich C kinase substrate (MARCKS), have been found to play crucial roles in neural plasticity.[98] In animal brains, tissue culture cells, and blood cells of bipolar patients, it has been shown that lithium treatment downregulates the activity of PKC and the expression of PKC isoforms α, ε, and ς in a time course that grossly parallels that of clinical improvement during the treatment. MARCKS was found to be downregulated by lithium treatment[99] and by valproic acid treatment.[100] The effect of lithium on MARCKS is more pronounced in the absence of inositol, consistent with the inositol hypothesis, whereas the effect of valproic acid on MARCKS is independent of the presence of inositol.[100] Among many signal transduction molecules that were found to be regulated by lithium, PKC and MARCKS are among the ones that were down-regulated by both lithium and valproic acid—2 mood-stabilizing agents that are chemically distinct—but not by carbamazepine. This may suggest that the regulation of PKC and MARCKS is a common final pathway for the therapeutic effect of at least some mood stabilizers (Table 3).

On the other hand, recent studies in neuronal cell systems have demonstrated no evidence for an effect of either acute or chronic lamotrigine on the regulation of the expression of either MARCKS or PKC isozymes (R.H.L.; C.-G.H.; L. Wang, M.D., Ph.D., unpublished data, Feb.

Table 3. Effects of Lithium, Valproic Acid, and Lamotrigine on PKC and MARCKS Signaling[a]

Variable	Lithium	Valproic Acid	Lamotrigine
PKC activity	Decrease	Decrease	ND
PKC α	Decrease	Decrease	NC
PKC ε	Decrease	Decrease	NC
MARCKS	Decrease	Decrease	NC

[a]Data from Manji and Lenox,[98] Lenox et al.,[99] and Watson et al.[100]
Abbreviations: MARCKS = myristoylated alanine-rich C kinase substrate, NC = no change, ND = not done, PKC = protein kinase C.

2004). It is generally accepted that the effect of mood-stabilizer treatment is associated with long-term changes in the biology of neurons, in which PKC and its substrate MARCKS are thought to play an important role. Our observation that lamotrigine and carbamazepine do not alter the expression of these molecules suggests that the effects of these mood-stabilizers are mediated by other pathways that will still result in long-term changes in cell biology.

PHARMACOKINETICS AND PHARMACODYNAMICS OF LAMOTRIGINE

The pharmacokinetics of lamotrigine have been studied in healthy volunteers,[101,102] in patients with epilepsy[103] or renal failure,[101] and in the elderly.[103] Lamotrigine pharmacokinetic parameters for adult patients and healthy volunteers are summarized in Table 4. The clearance of lamotrigine is affected by the coadministration of antiepileptic medications. Enzyme-inducing drugs such as carbamazepine, phenytoin, phenobarbital, and primidone increase clearance by more than 100% and decrease the half-life of lamotrigine by more than 50%, resulting in decreased plasma concentrations of lamotrigine.[105] When phenytoin is added to lamotrigine, the steady-state concentrations of lamotrigine decrease by approximately 45% to 54%, depending on the total dose of phenytoin.[103] Carbamazepine, phenobarbital, or primidone added to lamotrigine decrease lamotrigine steady-state concentrations by approximately 40%.[106] Conversely, enzyme-inhibiting drugs such as valproic acid reduce the clearance of lamotrigine by more than 50% and increase the half-life of lamotrigine by more than 100%, resulting in an increase in plasma lamotrigine concentration of slightly more than 2-fold.[107]

When lamotrigine is added to antiepileptic drug therapy, there is no appreciable effect on carbamazepine, phenytoin, phenobarbital, or primidone concentrations in plasma.[106] However, there may be an increased incidence of ataxia, blurred vision, diplopia, or dizziness in patients receiving carbamazepine with lamotrigine. One study[108] showed an increase in plasma carbamazepine epoxide (a toxic metabolite of carbamazepine) concentrations, but there are conflicting data on this finding.[109] The plasma concentration of valproic acid may decrease with concomitant lamotrigine.

When lamotrigine is given with both an enzyme-inducing antiepileptic drug and valproic acid, the lamotrigine half-life is approximately 30 hours.[110] These interactions are clinically significant: the usual starting dose of lamotrigine is 25 mg daily, but if the patient is taking concomitant valproic acid, the lamotrigine dose should be reduced to 12.5 mg daily.

Lamotrigine is rapidly and completely absorbed after oral administration, with negligible first-pass metabolism and an absolute bioavailability of 98%.[110] Absorption is not affected by food. Peak plasma concentrations occur anywhere from 1.4 to 4.8 hours after drug administration. Lamotrigine is widely distributed throughout the body, with the mean apparent volume of distribution following oral administration ranging from 0.9 to 1.3 L/kg.[111] The volume of distribution is independent of dose and is similar following single and multiple doses in patients with epilepsy and in healthy volunteers.

Data from in vitro studies indicate that lamotrigine is approximately 55% protein bound at plasma concentrations of 1 to 10 μg/mL.[110] Clinically significant interactions with other drugs through competition for protein binding sites are therefore unlikely. The binding of lamotrigine to plasma proteins did not change in the presence of therapeutic concentrations of phenytoin, phenobarbital, or valproic acid.[112] Lamotrigine was not found to displace carbamazepine, phenytoin, or phenobarbital from protein binding sites.[112]

Lamotrigine is metabolized predominantly by glucuronic acid conjugation; the major metabolite is an inactive 2-*N*-glucuronide conjugate. After oral administration of 240 mg of ^{14}C-labeled lamotrigine to 6 healthy volunteers, 94% was recovered in the urine and 2% in the feces.[103] The radioactivity in the urine consisted of unchanged lamotrigine (10%), the 2-*N*-glucuronide (76%), a 5-*N*-glucuronide (10%), a 2-*N*-methyl metabolite (0.14%), and other unidentified minor metabolites (4%).[103]

In healthy volunteers receiving no other medications and given single doses of lamotrigine ranging from 150 to 400 mg, the plasma concentrations of lamotrigine increased in direct proportion to the dose administered, suggesting that there is a linear relationship between dose and plasma concentrations.[102] The therapeutic range studied to date is 1 to 3 mg/mL, but the association between plasma concentration and efficacy or toxicity has not yet been established, and no guidelines have been established for patient monitoring based on plasma concentrations. A specific assay for the determination of lamotrigine concentrations in plasma is not readily available.

The clearance of lamotrigine does not appear to be affected by gender or age, but there are a few special populations in which lamotrigine has a different pharmacokinetic property. In non-Caucasians, the oral clearance of lamotrigine is 25% slower than in Caucasians.[110] In patients with renal insufficiency, clearance of lamotrigine

Table 4. Pharmacokinetic Parameters of a Single Dose or Multiple Doses of Lamotrigine in Adult Patients With Epilepsy or Healthy Volunteers[a]

	T_{max}, h		$T_{1/2}$, h		CL/F, mL/min/kg	
Study Population	Mean	Range	Mean	Range	Mean	Range
Patients also taking enzyme-inducing antiepileptic drugs[b]						
Single dose (N = 24)	2.3	0.5–5.0	14.4	6.4–30.4	1.10	0.51–2.22
Multiple doses (N = 17)	2.0	0.75–5.93	12.6	7.5–23.1	1.21	0.66–1.82
Patients also taking enzyme-inducing antiepileptic drugs + valproic acid						
Single dose (N = 25)	3.8	1.0–10.0	27.2	11.2–51.6	0.53	0.27–1.04
Patients also taking valproic acid only						
Single dose (N = 4)	4.8	1.8–8.4	58.8	30.5–88.8	0.28	0.16–0.40
Healthy volunteers also taking valproic acid						
Single dose (N = 6)	1.8	1.0–4.0	48.3	31.5–88.6	0.30	0.14–0.42
Multiple doses (N = 18)	1.9	0.5–3.5	70.3	41.9–113.5	0.18	0.12–0.33
Healthy volunteers taking no other medications						
Single dose (N = 179)	2.2	0.25–12.0	32.8	14.0–103.0	0.44	0.12–1.10
Multiple doses (N = 36)	1.7	0.5–4.0	25.4	11.6–61.6	0.58	0.24–1.15

[a]Adapted with permission from Perucca.[104] The majority of parameters' means determined in each study had coefficients of variation between 20% and 40% for $t_{1/2}$ and plasma clearance and between 30% and 70% for T_{max}. The overall mean values were calculated from individual study means that were weighted on the basis of the number of volunteers in each study. The numbers in parentheses below each parameter mean represent the range of individual volunteer/patient values across studies.
[b]Examples of enzyme-inducing antiepileptic drugs are carbamazepine, phenobarbital, phenytoin, and primidone.
Abbreviations: CL/F = plasma clearance, T_{max} = time to maximum plasma concentration, $T_{1/2}$ = elimination half-life.

is prolonged: the mean plasma half-life of lamotrigine was 42.9 hours in patients with chronic renal failure versus 26.2 hours in healthy volunteers.[101]

On the basis of available study data in women receiving concomitant oral contraceptive preparations, lamotrigine may be administered without significant pharmacokinetic interactions that potentially diminish contraceptive efficacy.[113] However, a recent case series of 7 women with epilepsy who received oral contraceptives while being treated with lamotrigine demonstrated that oral contraceptives reduced lamotrigine plasma levels by 41% to 64% (mean = 49%).[114] The authors concluded that women with epilepsy who are treated with both lamotrigine and oral contraceptives should have their lamotrigine plasma levels monitored closely; further study is required in women with bipolar disorder.

There are few safety data available on the use of lamotrigine in pregnancy, but there appears to be extensive placental transfer of lamotrigine. Lamotrigine is excreted in considerable amounts in breast milk, which in combination with slow elimination in infants may result in lamotrigine plasma concentrations in the infant comparable to those reported during active lamotrigine therapy.[115]

ADVERSE EFFECTS OF LAMOTRIGINE

The major adverse effects of lamotrigine that were observed in controlled monotherapy trials with bipolar patients are summarized in Table 5. Lamotrigine was well tolerated in these trials, with a frequency of side effects similar to that seen in patients receiving lamotrigine monotherapy for epilepsy treatment.[116] Headache and rash were the only adverse events that occurred more often with lamotrigine than with placebo. Concomitant medications, however, may change the frequency of side effects, for example rash, especially Stevens-Johnson syndrome and toxic epidermal necrolysis. Indeed, valproic acid seems to increase the risk of rash.[116,117] Ascher and colleagues[118] summarized side effects in double-blind, placebo-controlled acute depression and mania studies that were 3 to 10 weeks in duration. They found that the frequencies of nearly all adverse effects were the same for lamotrigine and placebo. However, rashes more often occurred with lamotrigine than with placebo (10% vs. 6%) in depression studies in which 602 patients received lamotrigine and 536 received placebo. Serious rashes occurred in 0.075% of patients in adult clinical trials by GlaxoSmithKline,[119] which is lower than the incidence in the epilepsy trials (0.18%). No occurrences of Stevens-Johnson syndrome were reported in the GlaxoSmithKline bipolar trials,[119] and 1 case of Stevens-Johnson syndrome was reported in an investigator-initiated trial.[30] Most recently, Calabrese and colleagues[8] reexamined the incidence of serious and nonserious rash in all controlled and open-label bipolar or unipolar trials in the GlaxoSmithKline database. They found the overall incidence of nonserious rash was 9.6% with lamotrigine and 7.1% with placebo in controlled monotherapy trials and 8.3% and 6.4% with lamotrigine and placebo, respectively, in all controlled trials.[8] The incidence of serious rash (Stevens-Johnson syndrome or toxic epidermal necrolysis) was 0% for lamotrigine and 0.1% with placebo. The authors emphasized that adhering to the manufacturer's recommended dosing titration may minimize the risk of serious rash.[8]

The incidence of rash with lamotrigine depends on the initial dose and on the rate of dose increase.[8,116,117] Approximately 2% of patients who were treated for seizure disorder with a starting lamotrigine dose of 25 mg/day

Table 5. Treatment-Emergent Side Effects of Lamotrigine in 5 Controlled Monotherapy Trials With Bipolar Patients (percentage of total patient groups experiencing effect) in the Randomized Phase

	Calabrese et al[29]		Calabrese et al[31]		Calabrese et al[33]; Bowden et al[34]		Frye et al[30]		Bowden et al[35,36]; Calabrese et al[37]	
Side Effects	Lamotrigine	Placebo	Lamotrigine	Placebo	Lamotrigine	Placebo	Lamotrigine	Placebo	Lamotrigine	Placebo
Any	79	92	67	68						
Headache	32–35	17	23	17	18	21	3	13	20	16
Infection	6	14	12	11	12	12			14	14
Pain	8–11	8	10	8						
Fatigue	2–5	6					0	3		
Influenza	2–3	6	7	9	8	11			10	6
Xerostomia	8	9								
Dizziness	9–10	14	9	3	8	10				
Somnolence	5	12			9	6			8	9
Insomnia	3–8	9			10	7			8	6
Ataxia/tremor					5	5	3	0		
Rhinitis	3	9								
Diplopia							0	3		
Abnormal dreams			2	1						
Nausea	16–17	15	14	11	17	12			7	9
Diarrhea	5	15			7	8	6	13	5	9
Dyspepsia	2–5	6								
Constipation	2–6	8								
Any rash	11–14	11	3	2	7	2	6	0	3	9
Pruritus	5–11	6								
Toxic epidermal necrolysis							1 case	0		
Back pain										

discontinued treatment, whereas approximately 40% of patients who received a starting dose of 200 mg/day discontinued treatment. The risk of rash is highest during the first 6 to 8 weeks of treatment with lamotrigine, peaking in the second week.[116] Females appear to be more vulnerable to rash than are males.[117]

If rash occurs, lamotrigine should be discontinued immediately pending a thorough dermatological examination. Examination of the patient by a dermatologist or primary care physician prior to initiation of lamotrigine may prevent spurious attribution to lamotrigine of a rash that had been present before treatment and improve the early diagnosis of newly occurring rash.

CONCLUSION

The therapeutic efficacy of lamotrigine in bipolar disorder is supported by numerous case reports, open-label studies, and double-blind, placebo-controlled studies, which have supported FDA approval of lamotrigine for the maintenance treatment of bipolar disorder. Recent studies strongly suggest the efficacy of lamotrigine for the treatment of acute depressive episodes as well as prophylaxis of recurrent depressive episodes in bipolar disorder; thus, these findings may support the notion that lamotrigine possesses unique therapeutic indication for bipolar depression. Since rapid-cycling bipolar disorder is often resistant to treatment and chronic or recurring depression is a therapeutic challenge, lamotrigine may have an important role in the treatment of bipolar disorder. Stevens-Johnson syndrome, the feared side effect of the medication, is clearly a concern, although it does not appear to occur as frequently as previously thought.

Understanding of the mechanisms underlying the mood-stabilizing effects of lamotrigine is far from complete as is the case for other mood stabilizers. Lamotrigine modulates activities of various ion channels and alters neuronal excitability. It is noteworthy that lamotrigine alters high-frequency firing and inhibits Na^+ channels in a voltage- and use-dependent manner. These mechanisms, by which lamotrigine normalizes supranormal neuronal activities are considered to be associated with its antiepileptic effects. It is noteworthy that the effects of lamotrigine on Na^+ channels are immediate and thus the time course of these effects is not consistent with that of therapeutic effects of lamotrigine. The use-dependent or activity-dependent nature of lamotrigine in decreasing firing or activities of neurons, however, can contribute to mood-stabilizing effects in collaboration with other mechanisms in which gene regulation is involved. Recent molecular studies suggested an association of accelerated intracellular signaling with bipolar disorder. In addition, several brain imaging studies have indicated increased metabolism or neuronal activities in certain brain regions of bipolar patients. Thus, the use-dependent inhibition of neuronal activity of lamotrigine, by decreasing abnormally high neuronal activities, while not affecting normal level of firing, may render the medication able to "stabilize mood" in bipolar disorder.

Most studies have been conducted on the acute effects of lamotrigine, and future studies should investigate the effects of lamotrigine on ion channels in a time frame that

is relevant to its clinical effects. The effects of lamotrigine on various elements of signal transduction mechanisms, such as phosphoinositol signaling, G proteins, PKC, and others, are yet to be elucidated. However, our study, in which lamotrigine treatment does not down-regulate the expression of PKC isoforms and MARCKS, suggests that lamotrigine might work through different mechanisms than do other mood stabilizers. Lamotrigine may have unique therapeutic effects, and investigating its action mechanisms may lead to a better understanding of various mechanisms that are associated with mood stabilization.

Drug names: acetazolamide (Diamox and others), carbamazepine (Tegretol, Carbatrol, and others), dextroamphetamine (Dexedrine, Dextrostat, and others), gabapentin (Neurontin and others), lamotrigine (Lamictal), lithium (Lithobid, Eskalith, and others), phenytoin (Dilantin, Phenytex, and others), primidone (Mysoline and others), topiramate (Topamax), trazodone (Desyrel and others), valproic acid (Depakene and others).

REFERENCES

1. Goodwin FK, Jamison KR. Manic-Depressive Illness. New York, NY: Oxford University Press, Inc; 1990
2. Lenox RH, Hahn CG. Overview of the mechanism of action of lithium in the brain: fifty-year update. J Clin Psychiatry 2000;61(suppl 9):5–15
3. Smith D, Baker G, Davies G, et al. Outcomes of add-on treatment with lamotrigine in partial epilepsy. Epilepsia 1993;34:312–322
4. Calabrese JR, Rapport DJ, Shelton MD, et al. Clinical studies on the use of lamotrigine in bipolar disorder. Neuropsychobiology 1998;38:185–191
5. Post RM, Denicoff KD, Frye MA, et al. A history of the use of anticonvulsants as mood stabilizers in the last two decades of the 20th century. Neuropsychobiology 1998;38:152–166
6. Bowden CL, Mitchell P, Suppes T. Lamotrigine in the treatment of bipolar depression. Eur Neuropsychopharmacol 1999;9(suppl 4):113–117
7. Berk M. Lamotrigine and the treatment of mania in bipolar disorder. Eur Neuropsychopharmacol 1999;9(suppl 4):119–123
8. 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;63:1012–1019
9. Weisler R, Risner M, Houser T. Use of lamotrigine in the treatment of bipolar disorder. Presented at the 147th annual meeting for American Psychiatry Association; May 21–26, 1994; Philadelphia, Pa
10. Calabrese JR, Fatemi SH, Woyshville MJ. Antidepressant effects of lamotrigine in rapid cycling bipolar disorder [letter]. Am J Psychiatry 1996;153:1236
11. Walden J, Hesslinger B, van Calker D, et al. Addition of lamotrigine to valproate may enhance efficacy in the treatment of bipolar affective disorder. Pharmacopsychiatry 1996;29:193–195
12. Fogelson DL, Sternbach H. Lamotrigine treatment of refractory bipolar disorder [letter]. J Clin Psychiatry 1997;58:271–273
13. Kusumakar V, Yatham LN. Lamotrigine treatment of rapid cycling bipolar disorder. Am J Psychiatry 1997;154:1171–1172
14. Kusumakar V, Yatham LN. An open study of lamotrigine in refractory bipolar depression. Psychiatry Res 1997;72:145–148
15. Sporn J, Sachs G. The anticonvulsant lamotrigine in treatment-resistant manic-depressive illness. J Clin Psychopharmacol 1997;17:185–189
16. Fatemi SH, Rapport DJ, Calabrese JR, et al. Lamotrigine in rapid-cycling bipolar disorder. J Clin Psychiatry 1997;58:522–527
17. Kotler M, Matar MA. Lamotrigine in the treatment of resistant bipolar disorder. Clin Neuropharmacol 1998;21:65–67
18. Bowden CL, Calabrese JR, McElroy SL, et al. The efficacy of lamotrigine in rapid cycling and non-rapid cycling patients with bipolar disorder. Biol Psychiatry 1999;45:953–958
19. Calabrese JR, Bowden CL, McElroy SL, et al. Spectrum of activity of lamotrigine in treatment-refractory bipolar disorder. Am J Psychiatry 1999;156:1019–1023
20. Suppes T, Brown ES, McElroy SL, et al. Lamotrigine for the treatment of bipolar disorder: a clinical case series. J Affect Disord 1999;53:95–98
21. Walden J, Schaerer L, Schloesser S, et al. An open longitudinal study of patients with bipolar rapid cycling treated with lithium or lamotrigine for mood stabilization. Bipolar Disord 2000;2:336–339
22. Berlant JL. Attention deficit hyperactivity disorder and bipolar disorder as predictors of clinical response to lamotrigine. Presented at the Second International Conference on Bipolar Disorder; June 19–21, 1997; Pittsburgh, Pa
23. Berlant JL. Case report of synergistic response of rapid cycling bipolar disorder to lamotrigine, risperidone and verapamil. Presented at the Second International Conference on Bipolar Disorder; June 19–21, 1997; Pittsburgh, Pa
24. Hoopes S, Snow M. Clinical effectiveness of lamotrigine in affective disorders. Presented at the Second International Conference on Bipolar Disorder; June 19–21, 1997; Pittsburgh, Pa
25. Ferrier IN, Potkins D, Eccleston D. Lamotrigine treatment of rapid cycling bipolar disorder: clinical and biological correlates. Presented at the Second International Conference on Bipolar Disorder; June 19–21, 1997; Pittsburgh, Pa
26. Mandoki M. Lamotrigine/valproate in treatment resistant bipolar disorder in children and adolescents. Presented at the annual meeting of the Society of Biological Psychiatry; May 15–17, 1997; San Diego, Calif
27. Mauri MC, Laini V, Somaschini E, et al. Lamotrigine: an alternative drug in the prophylaxis of bipolar disorder [abstract]. Eur Neuropsychopharmacol 1997;6:161
28. Nemeroff CB, Evans DL, Gyulai L, et al. Double-blind, placebo-controlled comparison of imipramine and paroxetine in the treatment of bipolar depression. Am J Psychiatry 2001;158:906–912
29. Calabrese JR, Bowden CL, Sachs GS, et al, for the Lamictal 602 Study Group. A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. J Clin Psychiatry 1999;60:79–88
30. 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;20:607–614
31. Calabrese JR, Suppes T, Bowden CL, et al, for the Lamictal 614 Study Group. A double-blind, placebo-controlled, prophylaxis study of lamotrigine in rapid-cycling bipolar disorder. J Clin Psychiatry 2000;61:841–850
32. Ichim L, Berk M, Brook S. Lamotrigine compared with lithium in mania: a double-blind randomized controlled trial. Ann Clin Psychiatry 2000;12:5–10
33. Calabrese JR, Bowden CL, Sachs G, et al. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. J Clin Psychiatry 2003;64:1013–1024
34. Bowden CL, Ghaemi SN, Gyulai L, et al. Lamotrigine delays mood episodes in recently depressed bipolar I patients (605 data). Presented at the 155th annual meeting of the American Psychiatric Association; May 18–23, 2002; Philadelphia, Pa
35. Bowden CL, Calabrese JR, Sachs G, et al. A randomized, placebo controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic bipolar I patients. Presented at the American College of Neuropsychopharmacology 40th Annual Meeting; December 9–13, 2001; Waikaloa, Hawaii
36. Bowden CL, Calabrese JR, Sachs G, et al. 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;60:392–400
37. Calabrese JR, Bowden C, DeVeaughy-Geiss J, et al. Lamotrigine demonstrates long-term mood stabilization in recently manic patients. Presented at the 154th annual meeting of the American Psychiatric Association; May 5–10, 2001; New Orleans, La
38. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382–389
39. Endicott J, Spitzer RL. A diagnostic interview: the schedule for affective disorders and schizophrenia. Arch Gen Psychiatry 1978;35:837–844
40. Bowden CL, Brugger AM, Swann AC, et al, for the Depakote Mania Study Group. Efficacy of divalproex vs lithium and placebo in the treatment of mania. JAMA 1994;271:918–924
41. Calabrese JR, Bowden L, Mee-Lee D, et al. Lamotrigine or lithium in the maintenance treatment of bipolar I disorder. Presented at the 155th annual meeting of the American Psychiatric Association; May 18–23, 2002; Philadelphia, Pa

42. Suppes P, Ascher JA, Bowden CL et al. Lamotrigine in rapid cycling bipolar disorder: predictors of response. Presented at the 154th annual meeting of the American Psychiatric Association; May 5–10, 2001; New Orleans, La
43. Gyulai L, Suppes T, Apter J, et al. Lamotrigine in rapid cycling bipolar disorder: predictors of response. Presented at the 41st Annual New Clinical Drug Evaluation Unit Meeting; May 28–31, 2001; Phoenix, Ariz
44. Spearing MK, Post RM, Leverich GS, et al. Modification of the Clinical Global Impressions (CGI) Scale for use in bipolar illness (BP): the CGI-BP. Psychiatry Res 1997;73:159–171
45. Cheung H, Kamp D, Harris E. An in vitro investigation of the action of lamotrigine on neuronal voltage-activated sodium channels. Epilepsy Res 1992;13:107–112
46. Lees G, Leach MJ. Studies on the mechanism of action of the novel anticonvulsant lamotrigine (Lamictal) using primary neurological cultures from rat cortex. Brain Res 1993;612:190–199
47. Xie X, Lancaster B, Peakman T, et al. Interaction of the antiepileptic drug lamotrigine with recombinant rat brain type IIA Na+ channels and with native Na+ channels in rat hippocampal neurones. Pflugers Arch 1995;430:437–446
48. Xiong ZQ, Stringer JL. Effects of felbamate, gabapentin and lamotrigine on seizure parameters and excitability in the rat hippocampus. Epilepsy Res 1997;27:187–194
49. Leach MJ, Marden CM, Miller AA. Pharmacological studies on lamotrigine, a novel potential antiepileptic drug, 2: neurochemical studies on the mechanism of action. Epilepsia 1986;27:490–497
50. Leach MJ, Baxter MG, Critchley MA. Neurochemical and behavioral aspects of lamotrigine. Epilepsia 1991;32(suppl 2):4–8
51 Kusumi I, Koyama T, Yamashita I. Thrombin-induced platelet calcium mobilization is enhanced in bipolar disorders. Biol Psychiatry 1992;32:731–734
52. Dubovsky SL. Calcium antagonists in manic-depressive illness. Neuropsychobiology 1993;27:184–192
53. Dubovsky SL, Christiano J, Daniell LC, et al. Increased platelet intracellular calcium concentration in patients with bipolar affective disorders. Arch Gen Psychiatry 1989;46:632–638
54. Wang SJ, Huang CC, Hsu KS, et al. Presynaptic inhibition of excitatory neurotransmission by lamotrigine in the rat amygdalar neurons. Synapse 1996;24:248–255
55. Wang SJ, Huang CC, Hsu KS, et al. Inhibition of N-type calcium currents by lamotrigine in rat amygdalar neurones. Neuroreport 1996;7:3037–3040
56. Stocker JW, Nadasdi L, Aldrich RW, et al. Preferential interaction of omega-conotoxins with inactivated N-type Ca2+ channels. J Neurosci 1997;17:3002–3013
57. Kuo CC, Lu L. Characterization of lamotrigine inhibition of Na+ channels in rat hippocampal neurones. Br J Pharmacol 1997;121: 1231–1238
58. Lang DG, Wang CM, Cooper BR. Lamotrigine, phenytoin and carbamazepine interactions on the sodium current present in N4TG1 mouse neuroblastoma cells. J Pharmacol Exp Ther 1993;266:829–835
59. Zona C, Avoli M. Lamotrigine reduces voltage-gated sodium currents in rat central neurons in culture. Epilepsia 1997;38:522–525
60. Xie X, Hagan RM. Cellular and molecular actions of lamotrigine: possible mechanisms of efficacy in bipolar disorder. Neuropsychobiology 1998;38:119–130
61. Ruben PC, Starkus JG, Rayner MD. Steady-state availability of sodium channels: interactions between activation and slow inactivation. Biophys J 1992;61:941–955
62. Dixon JF, Hokin LE. The antibipolar drug valproate mimics lithium in stimulating glutamate release and inositol 1,4,5-trisphosphate accumulation in brain cortex slices but not accumulation of inositol monophosphates and bisphosphates. Proc Natl Acad Sci U S A 1997;94:4757–4760
63. Dixon JF, Hokin LE. Lithium acutely inhibits and chronically up-regulates and stabilizes glutamate uptake by presynaptic nerve endings in mouse cerebral cortex. Proc Natl Acad Sci U S A 1998;95:8363–8368
64. Wang SJ, Sihra TS, Gean PW. Lamotrigine inhibition of glutamate release from isolated cerebrocortical nerve terminals (synaptosomes) by suppression of voltage-activated calcium channel activity. Neuroreport 2001;12:2255–2258
65. Conroy BP, Black D, Lin CY, et al. Lamotrigine attenuates cortical glutamate release during global cerebral ischemia in pigs on cardiopulmonary bypass. Anesthesiology 1999;90:844–854
66. Cunningham MO, Jones RS. The anticonvulsant, lamotrigine decreases spontaneous glutamate release but increases spontaneous GABA release in the rat entorhinal cortex in vitro. Neuropharmacology 2000;39:2139–2146
67. Teoh H, Fowler LJ, Bowery NG. Effect of lamotrigine on the electrically-evoked release of endogenous amino acids from slices of dorsal horn of the rat spinal cord. Neuropharmacology 1995;34: 1273–1278
68. Waldmeier PC, Baumann PA, Wicki P, et al. Similar potency of carbamazepine, oxcarbazepine, and lamotrigine in inhibiting the release of glutamate and other neurotransmitters. Neurology 1995;45:1907–1913
69. Braga MF, Aroniadou-Anderjaska V, Post RM, et al. Lamotrigine reduces spontaneous and evoked GABAA receptor-mediated synaptic transmission in the basolateral amygdala: implications for its effects in seizure and affective disorders: lamotrigine and inhibition in the amygdala. Neuropharmacology 2002;42:522–529
70. Anttila V, Rimpilainen J, Pokela M, et al. Lamotrigine improves cerebral outcome after hypothermic circulatory arrest: a study in a chronic porcine model. J Thorac Cardiovasc Surg 2000;120:247–255
71. Rimpilainen J, Romsi P, Pokela M, et al. Lamotrigine plus leukocyte filtration as a neuroprotective strategy in experimental hypothermic circulatory arrest. Ann Thorac Surg 2002;73:163–172
72. Garthwaite G, Brown G, Batchelor AM, et al. Mechanisms of ischaemic damage to central white matter axons: a quantitative histological analysis using rat optic nerve. Neuroscience 1999;94:1219–1230
73. Garthwaite G, Goodwin DA, Garthwaite J. Nitric oxide stimulates cGMP formation in rat optic nerve axons, providing a specific marker of axon viability. Eur J Neurosci 1999;11:4367–4372
74. Calabresi P, Picconi B, Saulle E, et al. Is pharmacological neuroprotection dependent on reduced glutamate release? Stroke 2000;31:766–772
75. Pisani F, Pedale S, Macaione V, et al. Neuroprotective effects of lamotrigine and remacemide on excitotoxicity induced by glutamate agonists in isolated chick retina. Exp Neurol 2001;170:162–170
76. Chen RW, Chuang DM. Long term lithium treatment suppresses p53 and Bax expression but increases Bcl-2 expression: a prominent role in neuroprotection against excitotoxicity. J Biol Chem 1999;274:6039–6042
77. Nonaka S, Chuang DM. Neuroprotective effects of chronic lithium on focal cerebral ischemia in rats. Neuroreport 1998;9:2081–2084
78. Nonaka S, Katsube N, Chuang DM. Lithium protects rat cerebellar granule cells against apoptosis induced by anticonvulsants, phenytoin and carbamazepine. J Pharmacol Exp Ther 1998;286:539–547
79. Chen G, Zeng WZ, Yuan PX, et al. The mood-stabilizing agents lithium and valproate robustly increase the levels of the neuroprotective protein bcl-2 in the CNS. J Neurochem 1999;72:879–882
80. Moore GJ, Bebchuk JM, Hasanat K, et al. Lithium increases N-acetyl-aspartate in the human brain: in vivo evidence in support of bcl-2's neurotrophic effects? Biol Psychiatry 2000;48:1–8
81. Manji HK, Moore GJ, Chen G. Lithium at 50: have the neuroprotective effects of this unique cation been overlooked? Biol Psychiatry 1999;46:929–940
82. Southam E, Kirkby D, Higgins GA, et al. Lamotrigine inhibits monoamine uptake in vitro and modulates 5- hydroxytryptamine uptake in rats. Eur J Pharmacol 1998;358:19–24
83. Shiah IS, Yatham LN, Lam RW, et al. Effects of lamotrigine on the 5-HT1A receptor function in healthy human males. J Affect Disord 1998;49:157–162
84. Manji HK, Potter WZ, Lenox RH. Signal transduction pathways: molecular targets for lithium's actions. Arch Gen Psychiatry 1995;52:531–543
85. Jope RS, Song L, Grimes CA, et al. Selective increases in phosphoinositide signaling activity and G protein levels in postmortem brain from subjects with schizophrenia or alcohol dependence. J Neurochem 1998;70:763–771
86. Lenox RH, McNamara RK, Papke RL, et al. Neurobiology of lithium: an update. J Clin Psychiatry 1998;59(suppl 6):37–47
87. Hallcher LM, Sherman WR. The effects of lithium ion and other agents on the activity of myo- inositol-1-phosphatase from bovine brain. J Biol Chem 1980;255:10896–10901
88. Sherman WR, Gish BG, Honchar MP, et al. Effects of lithium on phosphoinositide metabolism in vivo. Fed Proc 1986;45:2639–2646
89. Nahorski SR, Ragan CI, Challiss RA. Lithium and the phosphoinositide

cycle: an example of uncompetitive inhibition and its pharmacological consequences. Trends Pharmacol Sci 1991;12:297–303
90. Berridge MJ, Downes CP, Hanley MR. Neural and developmental actions of lithium: a unifying hypothesis. Cell 1989;59:411–419
91. Berridge MJ, Downes CP, Hanley MR. Lithium amplifies agonist-dependent phosphatidylinositol responses in brain and salivary glands. Biochem J 1982;206:587–595
92. Colin SF, Chang HC, Mollner S, et al. Chronic lithium regulates the expression of adenylate cyclase and Gi-protein alpha subunit in rat cerebral cortex. Proc Natl Acad Sci U S A 1991;88:10634–10637
93. Li PP, Tam YK, Young LT, et al. Lithium decreases Gs, Gi-1 and Gi-2 alpha-subunit mRNA levels in rat cortex. Eur J Pharmacol 1991;206: 165–166
94. Li PP, Young LT, Tam YK, et al. Effects of chronic lithium and carbamazepine treatment on G-protein subunit expression in rat cerebral cortex. Biol Psychiatry 1993;34:162–170
95. Klein PS, Melton DA. A molecular mechanism for the effect of lithium on development. Proc Natl Acad Sci U S A 1996;93:8455–8459
96. Chen G, Huang LD, Jiang YM, et al. The mood-stabilizing agent valproate inhibits the activity of glycogen synthase kinase-3. J Neurochem 1999;72:1327–1330
97. Nishizuka Y. Intracellular signaling by hydrolysis of phospholipids and activation of protein kinase C. Science 1992;258:607–614
98. Manji HK, Lenox RH. Ziskind-Somerfeld Research Award. Protein kinase C signaling in the brain: molecular transduction of mood stabilization in the treatment of manic-depressive illness. Biol Psychiatry 1999;46:1328–1351
99. Lenox RH, Watson DG, Patel J, et al. Chronic lithium administration alters a prominent PKC substrate in rat hippocampus. Brain Res 1992;570:333–340
100. Watson DG, Watterson JM, Lenox RH. Sodium valproate down-regulates the myristoylated alanine-rich C kinase substrate (MARCKS) in immortalized hippocampal cells: a property of protein kinase C-mediated mood stabilizers. J Pharmacol Exp Ther 1998;285: 307–316
101. Wootton R, Soul-Lawton J, Rolan PE, et al. Comparison of the pharmacokinetics of lamotrigine in patients with chronic renal failure and healthy volunteers. Br J Clin Pharmacol 1997;43:23–27
102. Cohen AF, Land GS, Breimer DD, et al. Lamotrigine, a new anticonvulsant: pharmacokinetics in normal humans. Clin Pharmacol Ther 1987;42:535–541
103. Armijo JA, Bravo J, Cuadrado A, et al. Lamotrigine serum concentration-to-dose ratio: influence of age and concomitant antiepileptic drugs and dosage implications. Ther Drug Monit 1999;21:182–190
104. Perucca E. The clinical pharmacokinetics of the new antiepileptic drugs. Epilepsia 1999;40(suppl 9):S7–S13
105. Benedetti MS. Enzyme induction and inhibition by new antiepileptic drugs: a review of human studies. Fundam Clin Pharmacol 2000;14: 301–319
106. Grasela TH, Fiedler-Kelly J, Cox E, et al. Population pharmacokinetics of lamotrigine adjunctive therapy in adults with epilepsy. J Clin Pharmacol 1999;39:373–384
107. Kanner AM, Frey M. Adding valproate to lamotrigine: a study of their pharmacokinetic interaction. Neurology 2000;55:588–591
108. Malminiemi K, Keranen T, Kerttula T, et al. Effects of short-term lamotrigine treatment on pharmacokinetics of carbamazepine. Int J Clin Pharmacol Ther 2000;38:540–545
109. Besag FM, Berry DJ, Pool F, et al. Carbamazepine toxicity with lamotrigine: pharmacokinetic or pharmacodynamic interaction? Epilepsia 1998;39:183–187
110. Garnett WR. Lamotrigine: pharmacokinetics. J Child Neurol 1997;12(suppl 1):10–15
111. Meyer FP, Banditt P, Schubert A, et al. Lamotrigine concentrations in human serum, brain tissue, and tumor tissue. Epilepsia 1999;40:68–73
112. Rambeck B, Wolf P. Lamotrigine clinical pharmacokinetics. Clin Pharmacokinet 1993;25:433–443
113. Wilbur K, Ensom MH. Pharmacokinetic drug interactions between oral contraceptives and second-generation anticonvulsants. Clin Pharmacokinet 2000;38:355–365
114. Sabers A, Buchholt JM, Uldall P, et al. Lamotrigine plasma levels reduced by oral contraceptives. Epilepsy Res 2001;47:151–154
115. Bar-Oz B, Nulman I, Koren G, et al. Anticonvulsants and breast feeding: a critical review. Paediatr Drugs 2000;2:113–126
116. Messenheimer J, Mullens EL, Giorgi L, et al. Safety review of adult clinical trial experience with lamotrigine. Drug Saf 1998;18:281–296
117. Wong IC, Mawer GE, Sander JW. Factors influencing the incidence of lamotrigine-related skin rash. Ann Pharmacother 1999;33:1037–1042
118. Ascher J, Barnett S, Batey S. Safety and tolerability of lamotrigine in controlled mood disorder trials. Presented at the 154th annual meeting of the American Psychiatric Association, May 5–10, 2001; New Orleans, La
119. Messenheimer JA, Ascher JA, Earl NL. New data confirming the importance of dosing and rash with lamotrigine. Presented at the 154th annual meeting of the American Psychiatric Association; May 5–10, 2001; New Orleans, La