A Placebo-Controlled 18-Month Trial of Lamotrigine and Lithium Maintenance Treatment in Recently Depressed Patients With Bipolar I Disorder

Joseph R. Calabrese, M.D.; Charles L. Bowden, M.D.; Gary Sachs, M.D.; Lakshmi N. Yatham, M.B.B.R., F.R.C.P.C., M.R.C.Psych.; Kirsten Behnke, M.D.; Olli-Pekka Mehtonen, M.D.; Paul Montgomery, Pharm.D.; John Ascher, M.D.; Walter Paska, Ph.D.; Nancy Earl, M.D.; and Joseph DeVeaugh-Geiss, M.D., for the Lamictal 605 Study Group

Background: The anticonvulsant lamotrigine was previously shown to be effective for bipolar depression. This study assessed the efficacy and tolerability of lamotrigine and lithium compared with placebo for the prevention of mood episodes in bipolar disorder.

Method: During an 8- to 16-week open-label phase, lamotrigine (titrated to 200 mg/day) was added to current therapy for currently or recently depressed DSM-IV–defined bipolar I outpatients (N = 966) and concomitant drugs were gradually withdrawn. Patients stabilized on open-label treatment (N = 463) were then randomly assigned to lamotrigine (50, 200, or 400 mg/day; N = 221), lithium (0.8–1.1 mEq/L; N = 121), or placebo (N = 121) monotherapy for up to 18 months. The primary outcome measure was time from randomization to intervention (addition of pharmacotherapy) for any mood episode (depressive, manic, hypomanic, or mixed). Data were gathered from September 1997 to August 2001.

Results: Time to intervention for any mood episode was statistically superior (p = .029) for both lamotrigine and lithium compared with placebo—median survival times were 200, 170, and 93 days, respectively. Intervention for depression was more frequent than for mania by a factor of nearly 3:1. Lamotrigine was statistically superior to placebo at prolonging the time to intervention for a depressive episode (p = .047). The proportions of patients who were intervention-free for depression at 1 year were lamotrigine 57%, lithium 46%, and placebo 45%. Lithium was statistically superior to placebo at prolonging the time to intervention for a manic or hypomanic episode (p = .026). The proportions of patients who were intervention-free for mania at 1 year were lamotrigine 77%, lithium 86%, and placebo 72%. Headache was the most frequent adverse event for all 3 treatment groups.

Conclusion: Lamotrigine and lithium were superior to placebo for the prevention of mood episodes in bipolar I patients, with lamotrigine predominantly effective against depression and lithium predominantly effective against mania.

(J Clin Psychiatry 2003;64:1013–1024)

Received Feb. 20, 2003; accepted June 20, 2003. *From the University Hospitals of Cleveland/Case Western Reserve University School of Medicine, Cleveland, Ohio (Dr. Calabrese); University of Texas Health Science Center at San Antonio (Dr. Bowden); Massachusetts General Hospital/Harvard University, Boston (Dr. Sachs); University of British Columbia, Vancouver, British Columbia, Canada (Dr. Yatham); Specialist practice, Frederiksburg, Denmark (Dr. Behnke); Psychiatric Clinic, University Hospital of Tampere, Pitkaniemi, Finland (Dr. Mehtonen); GlaxoSmithKline Research and Development, Research Triangle Park, N.C. (Drs. Montgomery, Ascher, Earl, and DeVeaugh-Geiss); and GlaxoSmithKline Research and Development, Greenford, United Kingdom (Dr. Paska).*

Dr. DeVeaugh-Geiss is now affiliated with the Department of Psychiatry, Duke University, Durham, N.C.

Supported by GlaxoSmithKline, Research Triangle Park, N.C.

Results presented in part at the 40th annual meeting of the American College of Neuropsychopharmacology, December 9–13, 2001, Waikoloa, Hawaii; the 155th annual meeting of the American Psychiatric Association, May 18–23, 2002, Philadelphia, Pa.; and the 15th annual congress of the European College of Neuropsychopharmacology, October 5–9, 2002, Barcelona, Spain.

Financial disclosure is listed at the end of this article.

The authors acknowledge the assistance of Gary Evoniuk, Ph.D., and Robin L. White, M.S., in analysis and interpretation of the data and preparation of this manuscript and the contributions of the Lamictal 605 Study Group, whose members are listed at the end of this article.

Corresponding author and reprints: Joseph R. Calabrese, M.D., University Hospitals of Cleveland/Case Western Reserve School of Medicine, Department of Psychiatry, 11400 Euclid Ave., Ste. 200, Cleveland, OH 44106 (e-mail: jrc8@po.cwru.edu).

Bipolar I disorder is a severely disabling illness that affects approximately 1.2% to 1.6% of the population.[1,2] Approximately 15% of patients with bipolar disorder will commit suicide.[3] The costs of both the illness and its associated disability rank bipolar disorder among the most costly illnesses. Wyatt and Hentner[4] estimated the annual U.S. costs of the illness to be $45 billion in 1990, more than the $40 billion spent on depression and, among mental illnesses, exceeded only by the $64 billion spent on schizophrenia.

Only 2 studies of maintenance treatment of bipolar disorder employing randomized, parallel-group, blinded, placebo-controlled designs with time-to-event analyses have been published.[5,6] Both studied patients enrolled during a manic episode. The second of the studies was designed in conjunction with the present study, which is the

first to investigate treatment outcomes of bipolar I patients enrolled during a current or recent depressive episode. This inquiry has important public health significance given long-term evidence from the National Institute of Mental Health Clinical Collaborative study that bipolar I patients experience depressive symptomatology approximately 3 times as frequently as hypomanic or manic symptoms.[7] In conjunction with the recently completed study of lamotrigine, placebo, or lithium therapy in recently manic patients, the present study allows the first opportunity to assess whether presenting episode type is associated with outcomes with 3 discrete treatments.

Lamotrigine, which is approved for the treatment of several forms of epilepsy and, more recently, as maintenance treatment in bipolar disorder, has been shown to be efficacious in a randomized, double-blind, placebo-controlled study in maintenance treatment of recently manic patients[6] as well as on a variety of endpoints in studies of bipolar depression[8,9] and rapid-cycling bipolar disorder.[10] The present study provides the first randomized trial to examine the efficacy and tolerability of lamotrigine and lithium compared with placebo in the maintenance treatment of bipolar I disorder patients who had recently experienced a depressive episode.

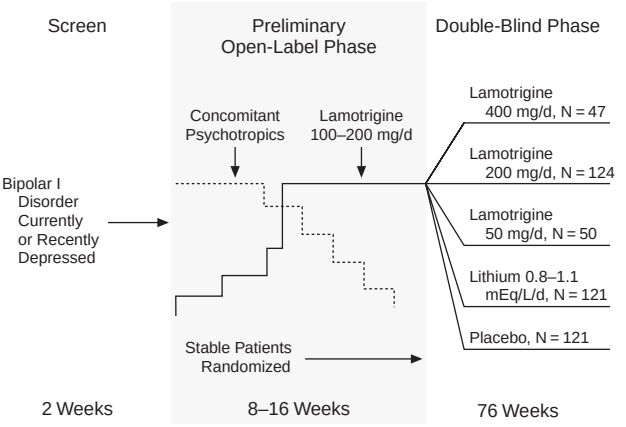
METHOD

This randomized, double-blind, parallel-group, placebo-controlled, multicenter study (Glaxo Wellcome protocol SCAB2003, GW605) was conducted at 79 centers in 15 countries from September 1997 to August 2001. An institutional review board or ethics committee approved the protocol at each study site, and all patients provided written informed consent prior to screening or study participation. Patients could be discontinued from any phase of the study for reasons including poor tolerance of study medication, lack of medication efficacy, pregnancy, investigator's or patient's unwillingness to continue the study for any reason, and noncompliance with study procedures. In all study phases, patients experiencing a rash when relationship to study drug could not be ruled out were to be discontinued from the study regardless of the severity of the rash.

Study Population

Patients aged at least 18 years with a diagnosis of bipolar I disorder were eligible for the study if they (1) were currently experiencing a major depressive episode as defined by the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (DSM-IV),[11] and ascertained by clinical interview, or if their most recent mood episode was a major depressive episode and occurred within 60 days of the screening visit with depressive symptoms still present at enrollment; (2) had at least 1 manic or hypomanic episode within 3 years of enrollment; and (3) had at least 1 additional depressed episode (including a mixed episode meeting DSM-IV criteria) within 3 years of enrollment. Patients were excluded if they had experienced more than 6 DSM-IV manic, hypomanic, mixed, or depressive episodes in the year prior to enrollment; had a DSM-IV diagnosis of, or had received treatment within the year prior to enrollment for, panic disorder, obsessive-compulsive disorder, social phobia, or bulimia nervosa; had a history of or current epilepsy; had clinically significant cardiac, renal, hepatic, neoplastic, or cerebrovascular disease; or if they were actively suicidal or had a score of ≥ 3 on item 3 (suicidality) of the Hamilton Rating Scale for Depression (HAM-D).[12]

Figure 1. Study Design for a Placebo-Controlled 18-Month Trial of Lamotrigine and Lithium Maintenance Treatment in Recently Depressed Patients With Bipolar I Disorder



Screening Phase

The screening phase occurred within 2 weeks prior to patients' entry into the open-label phase. Psychiatric and medical histories were obtained, physical examinations including clinical laboratory tests were performed, and scores on psychiatric rating scales including the 17-item HAM-D,[12] the 11-item Mania Rating Scale (MRS) from the Schedule for Affective Disorders and Schizophrenia–change version,[13] the Clinical Global Impressions-Severity of Illness and -Improvement scales (CGI-S, CGI-I),[14] and the Global Assessment Scale (GAS)[15] were recorded. Eligible patients were then enrolled in the open-label phase.

Open-Label Phase

During the 8- to 16-week open-label phase, any psychotropic medication was permitted to treat the ongoing depressive episode (Figure 1). All patients received open-label lamotrigine (target 200 mg/day with a minimum dose of 100 mg/day) adjunctively or as monotherapy

throughout this phase. All psychotropic medications other than lamotrigine were discontinued a minimum of 7 days prior to randomization. When lamotrigine was used as monotherapy, patients began a 6-week escalation of lamotrigine to a target dose of 200 mg/day (weeks 1–2, 25 mg/day; weeks 3–4, 50 mg/day; week 5, 100 mg/day; week 6, 200 mg/day). When used as adjunctive therapy with valproate, the lamotrigine starting and target doses were halved. When used as adjunctive therapy with carbamazepine, the lamotrigine starting and target doses were doubled. These concomitant antiepileptic drugs were tapered at the investigators' discretion so that patients received lamotrigine monotherapy at target doses for at least 1 week prior to the start of the double-blind phase. The lamotrigine dose was immediately doubled if valproate was discontinued and was gradually halved if carbamazepine was discontinued.

Adjunctive psychotropic medications used during the open stabilization phase were discontinued a minimum of 1 week (for oral antipsychotics, selective serotonin reuptake inhibitors [4 weeks for fluoxetine], tricyclic antidepressants, and benzodiazepines) to 2 weeks (for anticonvulsants, monoamine oxidase inhibitors, and reversible monoamine oxidase inhibitors) before entry into the double-blind phase. Lithium treatment could not be initiated during the open-label phase, and for those patients continuing ongoing lithium during the open-label phase, the dosage was tapered over at least 3 weeks and discontinued a minimum of 1 week prior to entering the double-blind phase of the study.

Clinic visits were scheduled weekly (or as necessary to ensure appropriate patient care) during the open-label phase. At each clinic visit, psychiatric evaluations from the screening visit were administered and patients were assessed for adverse events. Beginning at week 8 of the open-label phase, patients who had reached a stable dose of lamotrigine and met the criterion for randomization, defined as a CGI-S score of 3 (mildly ill) or lower maintained for at least 4 continuous weeks, were eligible to enroll in the double-blind phase of the study. Patients not meeting this criterion at the end of 16 weeks of open-label treatment were discontinued from the study.

Double-Blind Phase

Patients were initially randomly assigned with equal probability to 1 of 5 groups: lamotrigine (50, 200, or 400 mg/day), lithium (titrated to serum levels of 0.8–1.1 mEq/L), or placebo for up to 18 months (Figure 1). Double-blind double-dummy medications were identical in taste, appearance, and packaging. Monitoring and adjustment of lithium levels were performed by an unblinded central laboratory. All patients, regardless of treatment group, had serum drawn for lithium levels at no less than 8-week intervals (more frequently during the first 12 weeks). To maintain the blind, each instruction to adjust the lithium dose was accompanied by a corresponding instruction to adjust the lithium placebo dose in a lamotrigine and a placebo patient.

Clinic visits were scheduled weekly during the first 4 weeks of the double-blind phase, biweekly through week 8, and every 4 weeks thereafter through week 76. At each clinic visit, psychiatric evaluations from the screening visit were repeated and adverse events were assessed. Patients could be treated with added antidepressants, antipsychotics, anticonvulsants/mood stabilizers, or electroconvulsive therapy if the treating psychiatrist determined clinically that developing illness symptomatology required such additional intervention. The time to this treatment intervention was the primary outcome measure. However, short-term intermittent use of rescue medications was permitted, including the use of chloral hydrate (up to 2 g/day), lorazepam (up to 1 mg/day), temazepam (up to 10 mg/day), oxazepam (up to 30 mg/day), or midazolam (up to 15 mg/day) for control of agitation, irritability, restlessness, insomnia, or hostile behavior, without triggering the primary study endpoint. After reaching primary study endpoint, patients were permitted to continue double-blinded study medications and to receive augmentation treatment with open-label psychotropic medications other than lithium or lamotrigine up to week 52, and were then discontinued from the study. Patients who had not yet reached primary study endpoint were continued in the study through week 76.

Prior to enrollment of any patients, an a priori decision was made to combine the existing 200- and 400-mg/day lamotrigine groups for the primary analysis of efficacy. This decision was based on double-blind, placebo-controlled, dose-response data obtained from a previous trial, which showed less evidence of efficacy for the 50-mg dose.[8] Unless otherwise noted, efficacy and adverse event data are reported for the combined lamotrigine 200- and 400-mg/day groups. The latter data include adverse events that occurred following treatment intervention. Due to slow enrollment, the protocol was amended during the study to stop further enrollment into the lamotrigine 50- and 400-mg/day groups. Further assignment into the lithium, placebo, and lamotrigine 200-mg groups did not change. No unblinding or interim analysis was employed in the decision to implement this change.

Measures and Data Analysis

Efficacy. The primary efficacy endpoint was the time to intervention (addition of electroconvulsive therapy or pharmacotherapy, including antidepressants, antipsychotics, anticonvulsants/mood stabilizers, or benzodiazepines, the latter only at doses exceeding those allowed for rescue medication) for any mood (manic, hypomanic, mixed, or depressive) episode. The threshold for intervention was based on the investigators' overall clinical

judgment coupled with a general consensus agreement discussed and endorsed by investigators at a prestudy investigator meeting. Patients discontinuing from the study prior to intervention were either censored at the time of dropout (time to intervention) or categorized as treatment failures and considered to have had an event at the time of discontinuation (survival in study).

Secondary efficacy measures included time to intervention for a manic or hypomanic episode; time to intervention for a depressive episode; mean change from baseline (defined as day 1 of the double-blind phase) on the HAM-D, MRS, CGI-S, and GAS scores; and CGI-I scores during double-blind treatment. For the separate analyses of manic/hypomanic and depressed episodes, mixed episodes were assigned by the investigator to the predominating polarity for that episode, based on clinical judgment and verified by the appropriate rating scale data. For statistical analyses, the efficacy population comprised all patients randomized to treatment during the double-blind phase who received at least 1 dose of study medication and provided at least 1 post-baseline primary outcome assessment. Kaplan-Meier survival curves were generated for the time-to-event data, and differences among treatment groups were tested using log-rank tests at an $\alpha = .05$ level of significance. Due to the large number of investigator sites (N = 79), no adjustments were made for this factor, although exploratory analyses were carried out in an attempt to identify outlier sites.

Mean change scores for the psychiatric evaluations were compared between groups using analysis of variance on change from baseline scores at $\alpha = .05$, with treatment group as the only explanatory variable. Patient mean changes from randomization scores were calculated by giving missing values (i.e., due to missed visits or early termination) the mean of all observed values. Treatment group mean change scores were calculated as the average of all scores for each patient during the randomized phase. Differences between treatment groups in categorical variables were analyzed using the Fisher exact test. No interim analyses were performed on any of the study endpoints.

Sample size considerations. Prior to truncation of the 50-mg and 400-mg lamotrigine treatment groups, it was conservatively estimated that a minimum of 75 patients per group were required to detect a significant difference between treatment groups based on a projected incidence of depressive episodes of 65% for placebo and 40% for lamotrigine at a power of 0.8 and an alpha level of .025. Additional patients were enrolled to allow for dropouts and to ensure adequate power over the 18-month duration of the study.

Safety. The incidence of adverse events was summarized for each phase of the study for all patients who had received at least 1 dose of study medication during that phase. Laboratory and vital signs data were analyzed for frequency of clinically significant shifts. Safety data for lamotrigine were analyzed both separately and aggregately across the 3 dose groups with similar results. Serious rash was defined as any rash resulting in drug discontinuation and hospitalization.

RESULTS

Patients

Of 966 patients enrolled in the open-label phase, 480 completed this study phase, of whom 463 were randomly assigned to maintenance treatment during the double-blind phase (121 placebo, 121 lithium, 221 lamotrigine [50, 200, or 400 mg/day]; Table 1). Of the remaining patients who supplied any safety or efficacy data, 127 (13%) discontinued lamotrigine treatment due to adverse events and 54 (6%) discontinued due to failure to achieve randomization criteria. The most common adverse events leading to discontinuation from the open-label phase were rash (4%), mania (1%), and depression (1%). Seventeen patients completed the open-label phase but then withdrew consent to participate further.

Among patients randomly assigned to double-blind treatment, 3 (1 lithium, 2 lamotrigine) had no post-randomization safety assessments following entry into the double-blind phase of the study and were excluded from all safety analyses. Nine patients (2 placebo, 1 lithium, 4 lamotrigine 200 mg/day, 2 lamotrigine 400 mg/day) had no post-randomization efficacy assessments and were excluded from all efficacy analyses.

Other than intervention for a mood episode, the most common reasons for double-blind study phase discontinuation were adverse events (9% to 16%) and withdrawal of consent (9% to 11%). Other than a trend ($p = .076$) toward a higher rate of withdrawal due to adverse events for the lithium group compared with the lamotrigine group, rates of discontinuation classified by reason were similar across treatment groups (Table 1). Rates of discontinuation were also similar across the 3 lamotrigine dosage groups (data not shown).

Demographics and psychiatric history of patients enrolled in the double-blind safety population are summarized in Table 2. The patient sample had a mean age range of 42 to 44 years and had slightly more women than men. Nearly all patients had previously received medication for mood-related disturbance, with 61% having required psychiatric hospitalization and 35% having attempted suicide at some point in their lives. Depending on treatment group, 57% to 62% of patients had received prior lithium treatment at some point, with 67% to 72% of these patients having achieved good clinical response and 80% to 85% having tolerated such prior treatment (data not shown). Overall, demographic and disease characteristics of the sample were comparable across treatment groups.

Table 1. Disposition of Recently Depressed Bipolar I Disorder Patients, N (%)

Disposition	Open-Label Phase (N = 966)[a]	Double-Blind Phase (N = 463)[b] Placebo (N = 121)	Lithium (N = 121)	Lamotrigine (N = 221)[c]
Completed study phase	480 (50)	12 (10)	20 (17)	38 (17)
Intervention for a mood episode	…	66 (55)	56 (46)	115 (52)
Discontinued study prematurely	486 (50)	43 (36)	45 (37)	68 (31)
Failed to meet randomization criteria	54 (6)	…	…	…
Adverse event	127 (13)	12 (10)	19 (16)	20 (9)
Consent withdrawn	125 (13)	13 (11)	13 (11)	19 (9)
Lost to follow-up	60 (6)	7 (6)	5 (4)	13 (6)
Protocol violation	20 (2)	2 (2)	3 (2)	5 (2)
Other (including missing data)	100 (10)	9 (7)	5 (4)	11 (5)

[a]Eight patients in the open-label phase did not provide any post-screening safety assessments and were excluded from safety analyses. Two additional patients did not provide any post-screening efficacy assessments and were also excluded from efficacy analyses.
[b]Three patients (1 lithium, 2 lamotrigine) did not provide any post-randomization safety assessments and were excluded from safety analyses. Six (2 placebo, 4 lamotrigine) additional patients did not provide any post-randomization efficacy assessments and were also excluded from efficacy analyses.
[c]Includes all lamotrigine groups. Similar completion, intervention, and discontinuation rates were observed for the primary efficacy population of interest (lamotrigine 200- and 400-mg/day groups).

Table 2. Demographics and Disease Characteristics of Recently Depressed Bipolar I Disorder Patients

Characteristic	Open-Label Phase (N = 958)	Double-Blind Phase (N = 410)[a] Placebo (N = 121)	Lithium (N = 120)	Lamotrigine (N = 169)[a]
Demographics				
Age, mean (SD), y	42.2 (12.2)	42.1 (13.0)	43.6 (12.3)	44.1 (11.7)
Men, N (%)	370 (39)	61 (50)	48 (40)	70 (41)
Illness characteristics and treatment history				
History of psychotic episodes, N (%)[b]	300 (31)	36 (30)	35 (29)	49 (29)
Ever hospitalized for mood-related disturbances, N (%)[b]	628 (66)	78 (64)	76 (63)	96 (57)
Ever attempted suicide, N (%)[b]	353 (37)	43 (36)	42 (35)	59 (35)
Age at first depression, mean (SD), y	22.7 (11.6)	22.4 (11.9)	23.1 (12.1)	23.5 (11.8)
Age at first mania/mixed episode, mean (SD), y	26.7 (12.5)	25.7 (12.8)	28.4 (14.6)	27.7 (12.2)
No. of mood episodes in past year, mean (SD)				
Depression	1.7 (0.7)	1.8 (0.7)	1.7 (0.7)	1.6 (0.7)
Mania	0.9 (0.7)	1.0 (0.8)	0.9 (0.7)	0.7 (0.7)
Hypomania	0.3 (0.7)	0.3 (0.5)	0.3 (0.8)	0.3 (0.6)
Mixed	0.1 (0.4)	0.1 (0.6)	0.2 (0.5)	0.1 (0.3)
4–6 episodes in past year, N (%)	264 (28)	41 (34)	38 (32)	43 (25)

[a]Lamotrigine 200- and 400-mg/day groups combined.
[b]Remaining patients either were negative for presence of the parameter or had missing data.

The final median dose of lamotrigine in the open-label phase was 200 mg/day (range, 100–285 mg/day) both for all patients and for those eventually randomized. In addition to lamotrigine, other psychiatric medications were prescribed during the initial part of the open-label phase for 81% of all patients and 80% of those eventually randomized. Medications used by 10% or more of patients included antidepressants (44%), benzodiazepines (42%), lithium (20%), antipsychotics (18%), and valproate (13%). Use of these drugs was comparably distributed among the double-blind treatment groups, with the exception of a trend toward a greater use of antipsychotics during the preliminary phase for patients later randomly assigned to placebo (24%) compared with patients later randomly assigned to lithium (14%, p = .071). Fifty percent (480/966) of patients entering the initial open-label phase of the study achieved stabilization criteria and were eligible to enter the double-blind phase of the study, and 463 patients were ultimately randomized to treatment. In the double-blind phase, the final median dose for the lithium group was 900 mg/day (range, 450–1800 mg/day), which resulted in steady-state mean ± SD serum levels of 0.8 ± 0.3 mEq/L.

Time to Any Mood Episode

Median times to treatment intervention (with 95% confidence intervals [CIs]) were 93 days for placebo (95% CI = 58 to 180), 170 days for lithium (95% CI = 105 to not evaluable ["not evaluable" used when insufficient data are available to calculate upper end of CI]), and 200

Figure 2. Time to (A) Intervention for Any Mood Episode and (B) Discontinuation From Study: Kaplan-Meier Survival Curves

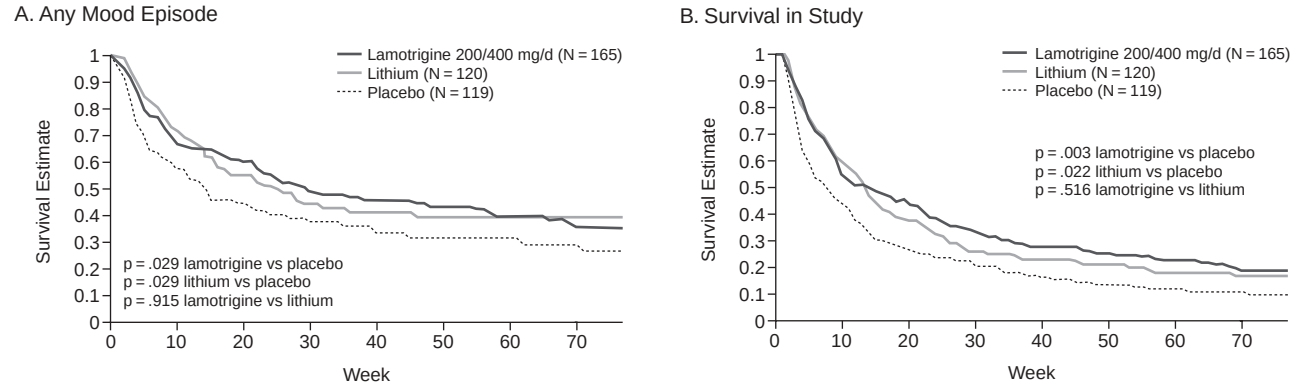
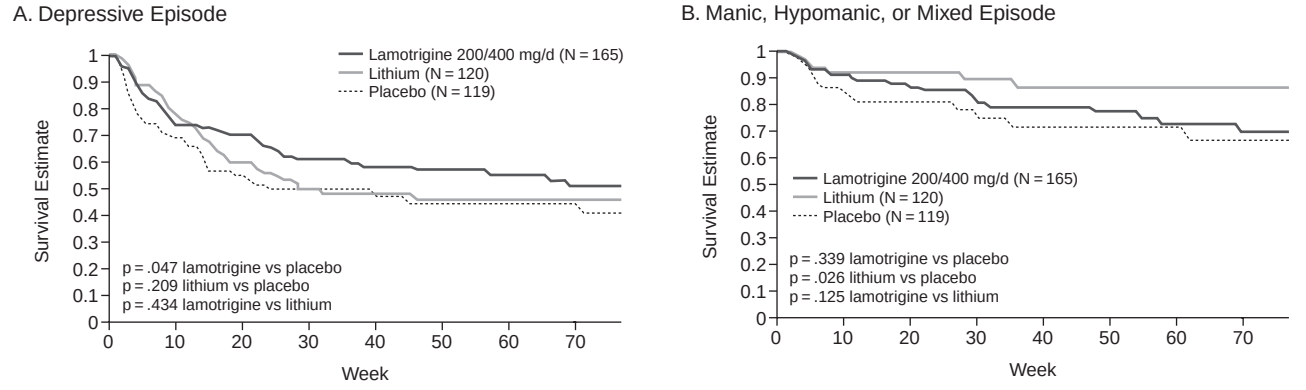


Figure 3. Time to Intervention for (A) Depressive Episode and (B) Manic, Hypomanic, or Mixed Episode: Kaplan-Meier Survival Curves



days for lamotrigine (95% CI = 146 to 399). On the primary endpoint, both lamotrigine and lithium were significantly superior to placebo at delaying time to intervention for any mood episode (p = .029 lamotrigine 200 and 400 mg/day vs. placebo; p = .029 lithium vs. placebo, Figure 2A). Lamotrigine and lithium did not differ from each other on this measure (p = .915). Similar results were obtained when only patients who had recently been treated with lithium were included in the analysis (in order to control for possible lithium discontinuation artifacts—data not shown).

On the analysis of overall survival in study (i.e., categorizing all early discontinuations as events), median times to treatment intervention (with 95% CIs) were 46 days for placebo (95% CI = 30 to 73), 86 days for lithium (95% CI = 63 to 111), and 92 days for lamotrigine (95% CI = 59 to 144). Both lamotrigine and lithium were significantly superior to placebo on this analysis of effectiveness (p = .003 lamotrigine vs. placebo; p = .022 lithium vs. placebo, Figure 2B). Lamotrigine and lithium did not differ from each other on this measure (p = .516). In the placebo group, 12/119 (10%) completed 18 months of monotherapy without treatment intervention versus 29/165 (18%) in the lamotrigine 200- and 400-mg/day groups (p = .053 vs. placebo) and 20/120 (17%) in the lithium group (p = .208 vs. placebo).

Medications added at the time of intervention (primary endpoint) included antidepressants (48% of patients requiring intervention), antipsychotics (18%), lamotrigine (15%), and benzodiazepines (12%). The distribution of medications used as treatment interventions was comparable across the treatment groups, except for more frequent use of antidepressants in the lithium group (59%) compared with the placebo group (36%, p = .018), more frequent use of lamotrigine as an intervention in the placebo group (24%) compared with the lamotrigine group (10%, p = .024), and a trend toward less frequent use of antipsychotics in the lithium group (9%) compared with the placebo (21%, p = .081) and lamotrigine (22%, p = .062) groups.

Table 3. Survival Data for Recently Depressed Bipolar I Disorder Patients

Efficacy Measure	Number of Events	Median Survival (days)	95% Confidence Interval	p Value vs Placebo[a]
Time to intervention for a mood episode				
Placebo (N = 119)	66	93	58, 180	N/A
Lithium (N = 120)	56	170	105, NE	.029
Lamotrigine 50 mg/d (N = 50)	32	118	64, 241	.634
Lamotrigine 200 mg/d (N = 120)	58	256	163, 482	.013
Lamotrigine 400 mg/d (N = 45)	25	144	49, 453	.571
Survival in study				
Placebo (N = 119)	107	46	30, 73	N/A
Lithium (N = 120)	99	86	63, 111	.022
Lamotrigine 50 mg/d (N = 50)	41	88	56, 151	.059
Lamotrigine 200 mg/d (N = 120)	96	105	59, 163	.001
Lamotrigine 400 mg/d (N = 45)	38	68	42, 144	.274
		1 Year, Intervention-Free Rate (%)[b]		
Intervention for depression				
Placebo (N = 119)	47	45	32, 57	N/A
Lithium (N = 120)	46	46	35, 58	.209
Lamotrigine 50 mg/d (N = 50)	20	49	33, 66	.413
Lamotrigine 200 mg/d (N = 120)	40	58	48, 69	.028
Lamotrigine 400 mg/d (N = 45)	17	54	36, 71	.533
Intervention for mania				
Placebo (N = 119)	19	72	59, 84	N/A
Lithium (N = 120)	10	86	77, 95	.026
Lamotrigine 50 mg/d (N = 50)	12	62	42, 82	.725
Lamotrigine 200 mg/d (N = 120)	18	79	69, 90	.237
Lamotrigine 400 mg/d (N = 45)	8	71	53, 89	.937

[a]Difference in survival distributions between treatments tested using a log-rank test.
[b]Median survival not calculable since some treatment groups never fell below 50% survival.
Abbreviations: N/A = not applicable, NE = not evaluable when insufficient data are available to calculate upper end of CI.

Time to Intervention for Depressive or Manic Symptoms

Among patients experiencing mood symptoms that required intervention during the double-blind phase, interventions for emerging symptoms of depression outnumbered interventions for manic symptoms by nearly 3:1. Interventions for mixed states were relatively infrequent (N = 15) and were counted as manic events, as this was considered to be the predominating polarity for all cases. Because some treatment groups had an insufficient number of depressive or manic events to calculate median survival times, Kaplan-Meier estimates of proportion of patients who were intervention-free for that polarity after 1 year of treatment are provided. The estimated proportions of patients without intervention for depression at 1 year were 45%, 46%, and 57% for placebo, lithium, and lamotrigine, respectively (full survival data are depicted in Figure 3A). Lamotrigine was superior to placebo on the key secondary endpoint of delaying intervention for depressive symptoms (p = .047 lamotrigine vs. placebo; p = .209 lithium vs. placebo; Figure 3A). Lamotrigine and lithium did not differ from each other on this measure (p = .434). The estimated proportions of patients without intervention for mania at 1 year were 72%, 86%, and 77% for placebo, lithium, and lamotrigine, respectively (full survival data are depicted in Figure 3B). Lithium was superior to placebo on the key secondary endpoint of delaying intervention for manic symptoms (p = .026 lithium vs. placebo; p = .339 lamotrigine vs. placebo; Figure 3B). Lamotrigine and lithium did not differ from each other on this measure (p = .125).

Table 3 summarizes median survival data for the separate lamotrigine 50-, 200-, and 400-mg dose groups, with lithium and placebo data for comparison. Compared with the placebo group, the lamotrigine 200-mg/day group had significantly prolonged survival on all measures except for time to intervention for an emerging manic or hypomanic episode. Neither the 50-mg nor the 400-mg/day dose groups differed significantly from the placebo group on any measure.

Changes in Symptom Severity and Overall Functioning

HAM-D and global rating scales at study entry reflected moderate severity of illness for both the overall population entering the open-label phase as well as those eventually randomized (Table 4). There were no apparent differences between double-blind treatment groups in illness severity at screening or randomization. Mean change-from-randomization scores for the HAM-D during the double-blind phase of the study indicated lesser degrees of worsening of depressive symptoms with lamo-

Table 4. HAM-D, MRS, GAS, and CGI Scores of Recently Depressed Bipolar I Disorder Patients[a]

	Placebo Group		Lithium Group		Lamotrigine Group[b]	
Scale	Patients	Mean (SD) Score	Patients	Mean (SD) Score	Patients	Mean (SD) Score
HAM-D (17-item)						
Screening (all patients)					943	23.4 (4.1)
Screening (randomized patients)	119	23.3 (4.0)	120	23.2 (4.5)	165	22.9 (4.1)
Randomization (baseline)	118	5.4 (4.0)	120	5.6 (4.6)	163	6.1 (4.4)
Mean change from baseline	115	4.9 (6.7)	120	2.9 (4.8)*	161	2.5 (5.3)*
MRS						
Screening (all patients)					943	2.0 (3.1)
Screening (randomized patients)	119	2.3 (3.8)	120	2.0 (3.2)	165	1.8 (2.7)
Randomization (baseline)	118	1.5 (2.7)	120	1.7 (2.7)	163	1.5 (2.8)
Mean change from baseline	115	1.1 (3.0)	120	0.7 (3.8)	161	0.7 (3.4)
GAS						
Screening (all patients)					941	49.7 (9.2)
Screening (randomized patients)	119	50.9 (9.1)	119	51.4 (10.5)	165	51.1 (9.2)
Randomization (baseline)	118	76.5 (11.4)	120	76.0 (10.4)	163	75.3 (11.8)
Mean change from baseline	115	–6.9 (11.1)	120	–4.1 (9.6)*	161	–2.8 (11.0)*
CGI-Severity of Illness						
Screening (all patients)					942	4.4 (0.7)
Screening (randomized patients)	119	4.4 (0.7)	119	4.3 (0.7)	165	4.3 (0.6)
Randomization (baseline)	118	2.0 (0.7)	120	2.0 (0.8)	163	2.0 (0.7)
Mean change from baseline	115	0.7 (1.0)	120	0.4 (0.9)*	161	0.3 (0.9)*
CGI-Improvement[c]						
Randomization (baseline)	118	1.7 (0.6)	120	1.7 (0.6)	163	1.7 (0.7)
Mean change from baseline	116	2.6 (1.1)	120	2.5 (1.2)	163	2.5 (1.3)

[a]Means calculated by giving missing values the mean of all observed values up to and including time of intervention.
[b]Lamotrigine 200- and 400-mg/day groups combined for randomized phase.
[c]Improvement rated relative to screening.
*$p < .05$ vs. placebo (repeated-measures analysis on all post-baseline data).
Abbreviations: CGI = Clinical Global Impressions scale, GAS = Global Assessment Scale, HAM-D = Hamilton Rating Scale for Depression, MRS = Mania Rating Scale.

trigine (200 and 400 mg/day) and lithium compared with placebo, with no significant difference between the 2 active treatment groups. Mean change scores for the MRS did not differ between any of the treatment groups. Mean change scores for both CGI-S and GAS during the double-blind phase of the study indicated lesser degrees of worsening in overall severity for both lamotrigine and lithium compared with placebo, with no significant difference between the 2 active treatment groups. None of the treatment groups differed significantly on CGI-I scores. Observed-case and last-observation-carried-forward results were similar. There were no differences between any of the treatment groups on the induction or worsening of manic symptoms (MRS-11 total score ≥ 10 at any time: 21%, 17%, and 20% for placebo, lithium, and lamotrigine, respectively; any increase in MRS-11 total score at any time: 61%, 51%, and 59%, respectively).

There were no significant differences between the percentage of patients in each treatment group who used benzodiazepines (placebo 19%, lithium 22%, lamotrigine 20%) or in the duration of such adjunctive therapy (100, 119, and 61 days, respectively).

Adverse Events

The most common treatment-emergent adverse event occurring during the open-label or double-blind phase was headache (Table 5). During the double-blind phase of the study, the incidence of headache was similar across treatment groups. The majority of adverse events were considered to be mild or moderate in intensity and resolved without sequelae, regardless of study phase. There did not appear to be a dose relationship for the incidence of adverse events in the 3 lamotrigine groups, with the possible exception of insomnia, which occurred in 6%, 10%, and 11% of patients in the lamotrigine 50-, 200-, and 400-mg/day groups, respectively (did not differ statistically from placebo). There were no serious rashes. The incidence of non-serious rash was significantly higher in the overall lamotrigine group (7%) compared with the placebo group (2%, 4.8% difference; 95% CI = 1.2 to 9.0). One case of mild Stevens-Johnson syndrome was reported in a patient with multiple risk factors while on lamotrigine treatment during the open-label phase. The patient did not require hospitalization and recovered uneventfully. The incidence of both tremor and somnolence was significantly elevated in the lithium group compared with the placebo group.

Adverse events led to the withdrawal of 127/966 patients from the open-label phase and 51/463 patients from the double-blind phase (placebo 10%, lithium 16%, lamotrigine 9%; $p = .076$ for lithium vs. lamotrigine, $p = .847$ for lamotrigine vs. placebo). The most frequent adverse event identified as leading to withdrawal from the open-label phase was non-serious rash (4% of patients). The most frequent adverse events leading to withdrawal from the double-blind phase were nausea (placebo 2%, lithium

Table 5. Recently Depressed Bipolar I Disorder Patients [N (%)] Reporting Common Adverse Events During Treatment[a]

Adverse Event	Open-Label Phase (N = 958)	Double-Blind Phase (N = 410)		
		Placebo (N = 121)	Lithium (N = 120)	Lamotrigine (N = 169)[b]
Headache	247 (26)	25 (21)	23 (19)	30 (18)
Nausea	127 (13)	15 (12)	24 (20)	28 (17)
Any rash	104 (11)	3 (2)	5 (4)	12 (7)*
Infection	110 (11)	14 (12)	14 (12)	21 (12)
Dizziness	101 (11)	12 (10)	13 (11)	14 (8)
Somnolence	83 (9)	7 (6)	16 (13)*	16 (9)
Diarrhea	81 (8)	10 (8)	19 (16)	12 (7)**
Insomnia	80 (8)	8 (7)	11 (9)	17 (10)
Influenza	72 (8)	13 (11)	10 (8)	13 (8)
Tremor	46 (5)	6 (5)	20 (17)*	9 (5)**

[a]Adverse events occurring in at least 10% of patients.
[b]Lamotrigine 200- and 400-mg/day groups combined.
*$p < .05$ vs. placebo.
**$p < .05$ vs. lithium.

7%, lamotrigine 1%), tremor (placebo 2%, lithium 6%, lamotrigine 1%), dizziness (placebo 2%, lithium 4%, lamotrigine 0%), and non-serious rash (placebo 1%, lithium 1%, lamotrigine 4%). For all but rash, the proportion of these lithium discontinuations was significantly higher than for lamotrigine. None of the lamotrigine discontinuation rates differed significantly from placebo.

The incidence of clinically significant abnormal laboratory values was low and did not suggest an effect of either of the active treatments, with 2 exceptions. Thyroid-stimulating hormone (TSH) levels increased in the lithium group but were relatively unchanged in the placebo and lamotrigine groups when expressed as both mean change from screening levels at weeks 28, 52, and 76 (placebo: –14%, –22%, –9%; lithium: +77%, +142%, +36%; lamotrigine: –8%, –7%, –16%, respectively) and the proportion of lithium patients (4%) with high TSH levels (prospectively defined as > 4.67 mU/L) compared with placebo or lamotrigine patients (0% in both cases). Mean total white blood cell counts increased in patients receiving lithium compared with placebo and lamotrigine (mean change from screening levels at weeks 28, 52, and 76: placebo +8%, +8%, 0%; lithium +18%, +26%, +26%; lamotrigine –1%, +1%, –5%, respectively), and there were more lithium patients with shifts from normal to high white blood cell counts (10% of lithium patients vs. 6% for placebo and 1% for lamotrigine). Week 76 observed mean changes in body weights from randomization were 1.2 kg (2.7 lb), 4.2 kg (9.3 lb), and –2.2 kg (–4.9 lb) for placebo, lithium, and lamotrigine, respectively (lamotrigine vs. lithium $p < .01$; comparisons with placebo were nonsignificant). The incidence of patients with 7% or greater increase in body weight at the final double-blind study visit was 6%, 10%, and 7% for the placebo, lithium, and lamotrigine groups, respectively.

There were 6 deaths among the 966 patients entering the study, including 4 suicides (3 men, 1 woman). Two of the suicides occurred during the open-label study phase, 1 occurred 3 weeks after discontinuation from the open-label phase, and 1 occurred approximately 6 weeks after randomization to lamotrigine 400 mg/day. None of the deaths were considered by the treating clinician to have a reasonable possibility of relationship to study medication. There were 11 other suicide attempts or gestures (10 in the open-label phase and 1 placebo patient in the double-blind phase). None of the suicide attempts were considered to be reasonably attributable to study medication except for 1 open-label phase patient whose change in depressive symptoms was also implicated by the treating clinician. The number of patients in each treatment group who ever had a score of 3 or greater on HAM-D item 3 (suicidality) during the double-blind phase was similar across the treatment groups (3 lamotrigine, 2 lithium, 1 placebo), and there were no significant differences between treatment groups on mean change scores for this item.

DISCUSSION

In this, the only large-scale maintenance study in recently depressed patients with bipolar I disorder completed to date, both lamotrigine and lithium monotherapy were significantly more effective than placebo at delaying the time to intervention for a mood episode, the primary efficacy measure of this study. Lamotrigine delayed the time to treatment for episodes of depression. Lithium delayed the time to treatment for episodes of mania. Neither drug exhibited evidence of worsening any phase of the illness. The results reported in this maintenance study were consistent across a variety of censoring methods.

Some aspects of the design of this maintenance study were novel. First, this study limited enrollment to recently depressed outpatients. Previously conducted maintenance studies in bipolar I disorder have typically limited enrollment to recently manic patients, usually hospitalized for acute mania. The only other placebo-controlled study of lithium in recently depressed patients with bipolar I disorder randomly assigned 18 patients to lithium, 13 to placebo, and 13 to imipramine.[16,17] Second, early maintenance studies[16,17,19–27] conducted in the 1970s evaluated the proportion of patients exhibiting a full relapse, usually severe enough to require hospitalization; earlier intervention was not permitted. The current study did not require hospitalization for the index episode. The primary endpoint, treatment intervention, was selected to improve the sensitivity of the primary outcome measure by lowering the threshold for a treatment "failure." This endpoint minimized patient exposure to placebo and spared patients the risks associated with full affective relapse. Even so, suicide attempts (4 completed) did occur in the current study, although at a rate comparable to that seen in other placebo-controlled studies of depression.[18] The current

study also provided clinically relevant information on the relative efficacy of the experimental treatments, albeit at the expense of potentially inflated treatment failure rates. The magnitude of the latter may also be due to the unmet treatment need in recently depressed patients, who may be more refractory to treatment and tend to relapse more frequently. This hypothesis is supported by recent findings that the proportion of time spent depressed versus manic was 3:1 in a cohort of bipolar I patients followed over a 10-year period.[7]

The design of this maintenance study had methodological limitations. First, comparisons between lithium and lamotrigine are problematic because of the study's unbalanced design.

Second, the a priori primary efficacy analysis for this study combined the 200- and 400-mg/day lamotrigine groups. Secondary analyses were planned to compare each of the 3 lamotrigine groups with placebo. Due to slow enrollment, the protocol was amended during the study to reduce the number of enrolling lamotrigine treatment groups from 3 to 1 (200 mg/day). As a result, only the 200-mg/day group was adequately powered to examine efficacy, which showed significant differences on all survival measures except time to intervention for mania.

Third, this and other studies have consistently excluded patients with comorbid anxiety disorders (except for generalized anxiety disorder), substance use disorders, or those currently suicidal, potentially limiting generalizability. Additional studies in patients with these and other comorbidities are clearly warranted.

Finally, and consistent with the methodology employed in many of the earliest lithium studies and every large bipolar maintenance study conducted in the past 30 years,[16,17,19–27] the current study employed an enriched double-blind discontinuation design in which patients who tolerated the experimental medicine under study (lamotrigine in this case) were eligible for randomization. The fact that all patients received open-label lamotrigine in the preliminary phase precludes a rigorous comparison of efficacy and adverse event rates between double-blind treatment groups assigned to lithium or lamotrigine, since some lamotrigine patients were eliminated due to intolerance or inefficacy during this initial phase.

This design continues to be used in the majority of maintenance studies in psychiatry because it decreases variance in the randomized population of patients and limits its exposure to placebo. That enrichment was unlikely to have introduced systematic bias in the current study is supported by the following lines of evidence: (1) a relatively small percentage of patients were eliminated from the preliminary phase due to lack of response (6%) or intolerance (13%) to lamotrigine, (2) less than 15% of the study population reported a history of difficulty tolerating lithium, (3) baseline illness severity, as assessed by psychiatric rating scale scores at study entry, did not differ significantly between patients who were eventually randomized and those who were not, (4) randomization criteria required only minimal improvement during the preliminary phase, and (5) patients were stabilized on a diverse variety of other medications in addition to lamotrigine.

Lithium was included as a treatment arm in this study to validate the study's design and findings. However, these results provide important new data corroborating the role of this agent in the treatment of bipolar disorder. In this study, lithium delayed time to intervention for mania but not for depression. Two large-scale placebo-controlled studies conducted by Prien and colleagues[16,19] combined with other published placebo-controlled maintenance studies[11,16,17,19–27] and the current study have demonstrated the usefulness of lithium as a maintenance therapy for bipolar I disorder. However, none of the earlier studies employed survival analytic techniques, which complement relapse rate analyses and have demonstrated in a placebo-controlled study for the first time that lithium also delays the onset of mood episodes in bipolar I disorder. Furthermore, the current study does not appear to have been confounded by lithium discontinuation artifacts. Lithium therapy could not be introduced during the preliminary phase, and any prior lithium therapy was tapered over a minimum 3-week period. Moreover, in a separate analysis of patients treated with lithium in the 5 months prior to randomization, both active treatment groups continued to separate statistically from placebo on the primary endpoint.

The long-term efficacy of lamotrigine has also been demonstrated in a similar study conducted in recently manic patients.[6] Moreover, both the previous and current studies produced a similar complementary pattern of results in which lithium delayed the time to treatment for episodes of mania but not depression and lamotrigine delayed time to treatment of depression but not mania. Neither drug exhibited evidence of worsening of any phase of the illness either in time to intervention or, for secondary efficacy measures, on mean change scores or proportion of patients with clinically significant worsening. The similarity in the pattern of results between the study reported herein and in previous studies, which enrolled patients who were recently manic, also suggests that the pattern of prophylactic efficacy of lamotrigine and lithium is not dependent on the polarity of the most recent mood episode. These data, combined with the results from previous studies, provide a body of evidence that supports the use of lamotrigine for the prophylaxis of depressive episodes in bipolar disorder.

Taken together with acute monotherapy data in bipolar I depressed patients,[8] which suggested numeric but not statistical superiority for 200 mg over 50 mg/day as well as efficacy data from 2 previous maintenance studies utilizing flexible lamotrigine dosing that resulted in an actual median dose near 200 mg/day,[6,10] the current data

suggest that 200 mg/day is a reasonable target dose for lamotrigine in the acute and maintenance treatment of bipolar disorder. Furthermore, the data from these and other previous studies do not suggest an increase in the incidence of lamotrigine-related adverse events with an increasing dose up to 200 mg/day. However, it is important to employ low starting doses and gradual escalation of lamotrigine in order to minimize the risk of serious rash.[28]

Although the depressive symptoms of bipolar disorder are associated with high morbidity, mortality, and overall burden,[3,7] few studies have focused on this aspect of the illness. There exists an urgent need to develop other medications that stabilize mood (both acutely and over the long term) by treating depressive symptoms associated with bipolar disorder.

CONCLUSION

In this large, randomized, 18-month study, lamotrigine and lithium were effective maintenance treatments for bipolar disorder, with lamotrigine primarily effective in preventing depressive episodes and lithium primarily effective in preventing manic episodes.

Drug names: carbamazepine (Tegretol, Epitol, and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), lamotrigine (Lamictal), lorazepam (Ativan and others), oxazepam (Serax and others), temazepam (Restoril and others).

Financial disclosure: Dr. Calabrese has been a consultant for, received grant/research support and honoraria from, and participated in speakers/advisory boards for GlaxoSmithKline. Dr. Bowden has been a consultant for Abbott Laboratories, GlaxoWellcome, Janssen, Lilly Research, Sanofi Synthelabo, and UCB Pharma, Inc.; has received grant/research support from Abbott Laboratories, Bristol-Myers Squibb, GlaxoWellcome, Janssen, Lilly Research, the National Institute of Mental Health, Parke-Davis, R. W. Johnson Pharmaceutical Institute, SmithKline Beecham, and the Stanley Foundation; and has participated in speakers bureaus for Abbott Laboratories, AstraZeneca, GlaxoWellcome, Janssen, Lilly Research, and Pfizer. Dr. Sachs has been a consultant for Abbott Laboratories, Glaxo Pharmaceuticals, Janssen, Eli Lilly, Bristol-Myers Squibb, Novartis, Elan, Sanofi, Sigma-Tau, and AstraZeneca; has received grant/research support from Abbott Laboratories and Janssen; and has received honoraria from Abbott Laboratories, Glaxo Pharmaceuticals, Janssen, Eli Lilly, Bristol-Myers Squibb, Solvay, Novartis, Sanofi, AstraZeneca, and Pfizer. Dr. Yatham has been a consultant for, received grant/research support and honoraria from, and participated in speakers/advisory boards for GlaxoSmithKline, Eli Lilly, Janssen-Cilag, and AstraZeneca. Dr. Ascher is an employee of and major stock shareholder in GlaxoSmithKline. Drs. Paska and Earl are employees of GlaxoSmithKline.

Members of the Lamictal 605 Study Group: Lawrence Adler, M.D., Glen Burnie, Md.; Lenard Adler, M.D., New York, N.Y.; Shaheen Akthar, M.D., Oslo, Norway; Raisa Andrezina, M.D., Ph.D., Tvaika, Latvia; Jeffrey Apter, M.D., Princeton, N.J.; Gregory Asnis, M.D., Bronx, N.Y.; Bjarne Bahr, M.D., Copenhagen, Denmark; David Baldwin, M.R.C.Psych, Southampton, U.K.; Mohammed Bari, M.D., Chula Vista, Calif.; Kirsten Behnke, M.D., Frederiksburg, Denmark; Charles Bowden, M.D., San Antonio, Tex.; Shlomo Brook, M.D., Krugersdorp, South Africa; Joseph Calabrese, M.D., Cleveland, Ohio; Charles Casat, M.D., Charlotte, N.C.; Amal Chakraburtty, M.D., Oklahoma City, Okla.; Guy Chouinard, M.D., Montreal, Quebec, Canada; Gerard Clerc, M.D., Pontorson, France; Lynn Cunningham, M.D., Springfield, Ill.; Abdallah Dallal, M.D., St. Jerome, Quebec, Canada; Rod Edwards, F.R.A.N.Z.C.P., Hastings, New Zealand; Richard Farmer, M.D., Memphis, Tenn.; Alan Feiger, M.D., Wheat Ridge, Colo.; Ronald Fieve, M.D., New York, N.Y.; Brent Forester, M.D., Meriden, N.H.; Allen Fraser, M.D., Takapuna, New Zealand; Thomas George, F.R.A.N.Z.C.P., Brisbane, Australia; S. Nassir Ghaemi, M.D., Washington, D.C.; Francis Gheysen, M.D., Cannes, France; Lawrence Ginsberg, M.D., Houston, Tex.; Laslo Gyulai, M.D., Philadelphia, Pa.; David Hellerstein, M.D., New York, N.Y.; Ole Høyberg, M.D., Molde, Norway; Leighton Huey, M.D., Farmington, Conn.; Robin Jacobson, M.D., London, U.K.; Zoltan Janka, Ph.D., Semmelweis, Hungary; Riitta Jokinen, M.D., Turku, Finland; Siegfried Kasper, M.D., Vienna, Austria; Kenneth Kaufman, M.D., New Brunswick, N.J.; Sidney Kennedy, M.R.C.Psych, Toronto, Canada; Rakhshan Kermani, M.B.B.S., London, U.K.; Arifulla Khan, M.D., Bellevue, Wash.; Olav Knudsen-Baas, M.D., Arendal, Norway; Irving Kolin, M.D., Winter Park, Fla.; Kai Konsap, M.D., Tallinn, Estonia; Vivek Kusumakar, M.R.C.Psych, Halifax, Nova Scotia, Canada; Tarja Lämsä, M.D., Oulu, Finland; Robert Levine, M.D., New York, N.Y.; Bruce Lydiard, M.D., Ph.D., Charleston, S.C.; Barry Maletzsky, M.D., Portland, Ore.; Denis Mee-Lee, M.D., Honolulu, Hawaii; Olli-Pekka Mehtonen, M.D., Pitkaniemi, Finland; Adam Moscovitch, M.D., Calgary, Alberta, Canada; Hannu Naukkarinen, M.D., Helsinki, Finland; Bjarne Nielson, M.D., Copenhagen, Denmark; Dag Norum, M.D., Fredrikstad, Norway; Jorg Pahl, M.D., Oklahoma City, Okla.; Mark Rapaport, M.D., San Diego, Calif.; Stig Rasmussen, M.D., Hillerød, Denmark; Frederick Reimherr, M.D., Salt Lake City, Utah; Zoltan Rihmer, Ph.D., Hüvösvölgyi, Hungary; Hans Rittmannsberger, M.D., Linz, Austria; Diego Rosales, M.D., Sherbrooke, Quebec, Canada; Alan Rosenbaum, M.D., Farmington Hills, Mich.; Anthony Rothschild, M.D., Worcester, Mass.; Frédéric Rouillon, M.D., Colombes, France; Georges Ruetsch, M.D., Poitiers, France; Simo Saarijärvi, M.D., Turku, Finland; Gary Sachs, M.D., Boston, Mass.; Martha Sajatovic, M.D., Brecksville, Ohio; Jean-Claude Samuelian, M.D., Marseille, France; Pål Sandvik, M.D., Levanger, Norway; Jeffrey Simon, M.D., Brown Deer, Wis.; Amarendra Singh, M.R.C.Psych, Coventry, U.K.; Jesper Soegaard, M.D., Frederiksburg, Denmark; Christoph Stuppaeck, M.D., Salzburg, Austria; Alan Swann, M.D., Houston, Tex.; Ivana Timotijevic, M.D., Ph.D., Belgrade, Yugoslavia; Laslo Tringer, Ph.D., Balassa, Hungary; Frank Varghese, F.R.A.N.Z.C.P., Woolongabba, Australia; Scott West, M.D., Orlando, Fla.; Don Wilson, M.Med, Cape Town, South Africa; Lakshmi Yatham, M.B.B.R., F.R.C.P.C., M.R.C.Psych., Vancouver, British Columbia, Canada; Trevor Young, M.D., Ph.D., Hamilton, Ontario, Canada; and John Zajecka, M.D., Chicago, Ill.

REFERENCES

1. Regier DA, Narrow WE, Rae DS, et al. The de facto US mental and addictive disorders service system: epidemiologic catchment area prospective 1-year prevalence rates of disorders and services. Arch Gen Psychiatry 1993;50:85–94
2. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. Arch Gen Psychiatry 1994;51:8–19
3. Goodwin FK, Jamison KR. Suicide. In: Manic-Depressive Illness. New York, NY: Oxford University Press; 1990:227–243
4. Wyatt RJ, Hentner I. An economic evaluation of manic-depressive illness: 1991. Soc Psychiatry Psychiatr Epidemiol 1995;30:213–219
5. Bowden CL, Calabrese JR, McElroy S, et al. A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. Arch Gen Psychiatry 2000;57: 481–489
6. 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
7. Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry 2002;59:530–537
8. Calabrese JR, Bowden CL, Sachs GS, et al, for the Lamictal 602 Study Group. A double-blind, placebo-controlled study of lamotrigine mono-

therapy in outpatients with bipolar I depression. J Clin Psychiatry 1999;60:79–88
9. 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
10. Calabrese JR, Suppes T, Bowden CL, et al. A double-blind, placebo-controlled, prophylaxis study of lamotrigine in rapid-cycling bipolar disorder. J Clin Psychiatry 2000;61:841–850
11. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
12. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
13. Endicott J, Spitzer RL. A diagnostic interview: the Schedule for Affective Disorders and Schizophrenia. Arch Gen Psychiatry 1978;35:837–844
14. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
15. Endicott J, Spitzer RL, Fleiss JL, et al. The Global Assessment Scale: a procedure for measuring overall severity of psychiatric disturbance. Arch Gen Psychiatry 1976;33:766–771
16. Prien RF, Klett CJ, Caffey EM Jr. Lithium carbonate and imipramine in prevention of affective episodes: a comparison in recurrent affective illness. Arch Gen Psychiatry 1973;29:420–425
17. Prien RF, Klett CJ, Caffey EM Jr. Lithium prophylaxis in recurrent affective illness. Am J Psychiatry 1974;131:198–202
18. Khan A, Warner HA, Brown WA. Symptom reduction and suicide risk in patients treated with placebo in antidepressant clinical trials. Arch Gen Psychiatry 2000;57:311–317
19. Prien RF, Caffey EM Jr, Klett CJ. Prophylactic efficacy of lithium carbonate in manic-depressive illness: report of the Veterans Administration and National Institute of Mental Health collaborative study group. Arch Gen Psychiatry 1973;28:337–341
20. Baastrup PC, Poulsen J, Schou M, et al. Prophylactic lithium: double-blind discontinuation in manic-depressive and recurrent depressive disorders. Lancet 1970;2:326–330
21. Melia PI. Prophylactic lithium: a double-blind trial in recurrent affective disorders. Br J Psychiatry 1970;116:621–624
22. Coppen A, Noguera R, Bailey J, et al. Prophylactic lithium in affective disorders: controlled trial. Lancet 1971;2:275–279
23. Small JG, Small IF, Moore DF. Experimental withdrawal of lithium in recovered manic-depressive patients: a report of five cases. Am J Psychiatry 1971;127:1555–1558
24. Hullin RP, McDonald R, Allsopp MN. Prophylactic lithium in recurrent affective disorders. Lancet 1972;1:1044–1046
25. Cundall RL, Brooks PW, Murray LG. A controlled evaluation of lithium prophylaxis in affective disorders. Psychol Med 1972;2:308–311
26. Stallone F, Shelley E, Mendlewicz J, et al. The use of lithium in affective disorders: a double-blind study of prophylaxis in bipolar illness. Am J Psychiatry 1973;130:1006–1010
27. Fieve RR, Kumbarci T, Dunner DL. Lithium prophylaxis for depression in bipolar I, bipolar II, and unipolar patients. Am J Psychiatry 1976;133: 925–929
28. Wong ICK, Mawer GE, Sander JWAS. Factors influencing the incidence of lamotrigine-related skin rash. Ann Pharmacother 1999;33:1037–1042

