Mood Stabilization and Destabilization During Acute and Continuation Phase Treatment for Bipolar I Disorder With Lamotrigine or Placebo

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Background: During post–acute phase pharmacotherapy for bipolar disorder, there has been little empirical study to establish when emerging mania symptoms (1) are of clinical significance and (2) reflect iatrogenic events versus the natural course of illness.

Method: Secondary analyses were conducted in a previously studied group of bipolar I disorder (*DSM-IV*) outpatients randomly assigned to lamotrigine monotherapy (n = 171) or placebo (n = 121), and a larger prerandomization group (N = 966) during open-label titration of lamotrigine, following an index depressive episode. Time until the emergence of mania symptoms, at varying severity thresholds, was examined over 6 months for lamotrigine versus placebo, while controlling for potential confounding factors in Cox proportional hazard models. Subject enrollment occurred between July 1997 and August 2001.

Results: Rates of mood elevation during both acute open-label and randomized continuation phases of lamotrigine treatment were comparable to those seen with placebo during the randomized phase. The hazard ratio for the emergence of mania symptoms with lamotrigine was not significantly different from placebo (hazard ratio = 0.79; 95% CI, 0.53 to 1.16), with an upper bound that suggests no meaningful increase in susceptibility toward mania with lamotrigine. By contrast, clinically meaningful rises in mania symptom severity were predicted by baseline residual manic symptoms prerandomization and by the number of manic, hypomanic, or mixed episodes in the past year.

Conclusions: Based on a composite definition of mood destabilization involving a range of severity thresholds for emerging signs of mania, lamotrigine confers no meaningful elevated risk relative to placebo for mood destabilization in bipolar I disorder. Rather, illness burden related to residual or lifetime mania features may hold greater importance for explaining mania relapses or breakthrough manic features during lamotrigine continuation pharmacotherapy.

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Central to the concept of mood stabilization for bipolar disorder is the principle that treatments neither exacerbate nor induce the opposite polarity of illness.[1,2] Uncertainties persist about the extent to which antidepressants may precipitate mania,[3–5] particularly tricyclic[3] and other noradrenergic antidepressants.[6] At least some second-generation antipsychotics may have the potential to sporadically induce mania acutely,[7] although controlled trials show no greater risk with olanzapine or aripiprazole than placebo for the emergence of mania during continuation or maintenance phases of therapy.[8,9]

The term *mood destabilization* has been used to describe clinical worsening of illness course due to exacerbations of affective episodes with opposite polarity to an index episode.[10,11] Acutely, destabilization may occur as a polarity switch after recent exposure to a psychotropic agent (eg, the concept of antidepressant-induced mania). Longitudinally, destabilization may involve the acceleration of cycling frequency, the progression of subsyndromal symptoms, or an increased illness burden associated with the opposite polarity of the index episode.

An obstacle to clinical and research efforts has been the lack of an empirically-derived operational definition for mood destabilization. No universal convention exists for defining either acute "switch" events into mania or hypomania or longer-term cycle acceleration.[11] Some investigators have adopted an operational definition of Young Mania Rating Scale scores of 15 or greater to identify cases of treatment-emergent mania/hypomania.[12] Others have relied on fulfillment of *DSM-IV* or similar symptom- and duration-based criteria for a manic or hypomanic episode in order to define "switch,"[6] while still others use standardized terminology (eg, the Medical Dictionary for Regulatory Activities; MedDRA[13]) capturing "euphoria" as an adverse event.

Until recently, efforts to study long-term mood destabilization in bipolar disorder have been hampered by the

scarcity of randomized maintenance pharmacotherapy trials that standardize the polarity of the index episode. The importance of such standardization stems from prior observations that the polarity of an index episode predicts the polarity of short-term relapse,[14] thereby confounding efforts to distinguish iatrogenic mood destabilization from the natural course of illness.

The main goal of the present study was to examine the extent of "upward drift" from euthymia toward mania at varying symptom severity levels in a group of bipolar outpatients whose most recent episode polarity was depression. Data were utilized from a previously reported maintenance pharmacotherapy trial with lamotrigine, an anticonvulsant with longitudinal efficacy against either polarity of illness relative to placebo for bipolar I disorder. Two 18-month randomized trials found no overall increased risk for the emergence of mania or hypomania as an adverse event with lamotrigine than placebo.[15] However, its putative antidepressant properties,[2,16,17] presence of antiglutamatergic and absence of γ-aminobutyric acid (GABA)-ergic effects,[18] and more robust efficacy against recurrent depressive than manic episodes,[15] raise at least theoretical concern about its potential for inducing mood elevation. Anecdotal reports in the literature have reinforced such apprehension.[19] To better elucidate current uncertainties about risk for mood destabilization, the present study utilized data from the continuation phase of a previously reported randomized, placebo-controlled relapse prevention trial. Two specific aims were addressed: (1) to identify clinically meaningful thresholds of emerging mania symptoms during continuation-phase pharmacotherapy for bipolar I disorder, and (2) to provide more definitive information about the safety versus risk for lamotrigine to induce manic or hypomanic symptoms, relative to potential confounding factors, in patients with bipolar I disorder over a 6-month period.

METHOD

As described in greater detail previously,[20] the study group was composed of 463 adults (ages 18 and over) with bipolar I disorder (*DSM-IV*) who originally underwent up to 18 months of randomized treatment with lamotrigine or placebo after an open-label acute stabilization phase. These randomized subjects were derived from a larger group of 966 bipolar I disorder patients who were ascertained based on having had a depressive episode within 60 days of the initial screening visit and subsequently underwent initial open-label treatment with lamotrigine for 8 to 16 weeks, as reported elsewhere.[20] Notably, subjects from the original study with an index episode polarity of either mania/hypomania or mixed episodes[15] were excluded from the present analyses in order to focus on the emergence of new mania symptoms after an acute bipolar depressive episode. Because patients with recent mania are more prone to relapse into mania than depression,[14] we further sought to minimize detection of artificially inflated mania symptoms (due to relapse of an index mania), focusing instead on the development of new mania symptoms after a depressive episode, in the first several months after randomization.

Sample sizes for the randomized phase were based on the "percentage of subjects experiencing a relapse or recurrence of a depressive episode" (PRD). A minimum of 75 subjects per group was determined sufficient to detect a statistically significant difference between lamotrigine and placebo treatment groups in PRD with 80% power. This assumed a PRD for the placebo population of 65% and a PRD of 40% for the lamotrigine population, and a significance level of .025, using the Bonferroni adjustment for 2 comparisons: lamotrigine 200 mg versus placebo, and lamotrigine 400 mg versus placebo. Assuming an approximate 25% dropout rate, a total of 100 subjects per group were to be enrolled into the randomized phase. No interim analyses were planned or conducted. Subject enrollment occurred between July 12, 1997, and August 9, 2001.

Randomization codes were computer-generated at GlaxoSmithKline. Each site was initially assigned 10 treatment numbers, ie, 2 permuted blocks of 5 treatments each. On entering the randomized phase, subjects were assigned a treatment number, based on lithium use in the 5-month period before enrollment in the study. Subjects with no lithium treatment within 5 months of screen were assigned by the investigator to the lowest available treatment number, and subjects who had been treated with lithium within 5 months were assigned the highest available treatment number, thereby addressing the balance of treatment assignments within these 2 subgroups. In the event of a subject withdrawing from the study once randomized assignment had occurred, that treatment number was not reassigned. Subjects and investigators were blinded to treatment arm status.

During the randomized phase, study subjects, those administering study medication, and those assessing the outcomes were blinded to treatment group assignment. Breaking the blind by opening the hidden portion of the detachable portion of the label or disclosure envelop was forbidden, except in the event of a medical emergency. "Major protocol deviations" were defined as deviations from the study protocol that could have adversely affected the assessment of efficacy. Clinical Development, in consultation with the project medical advisor, was responsible for defining the appropriate set of major protocol deviations and conducting a blinded review of the data to identify subjects with significant deviations. Any unforeseen circumstance that occurred during the study period was reviewed on an individual basis to determine whether it constituted a major protocol deviation. Based on this review, 30 of the 463 randomized subjects (6%) were identified as having major protocol deviations.

Subjects were eligible to undergo randomization after 8 weeks if they achieved a Clinical Global Impressions-Severity of Illness[21] scale score of 3 ("mildly ill") or lower,

maintained for at least 4 continuous weeks. The study group during the double-blind randomized phase was enriched for subjects who demonstrated initial stabilization with lamotrigine open-label monotherapy for at least 1 week after discontinuation of prestudy psychotropic medications. Mania symptoms were rated using the 11-item Mania Rating Scale (MRS-11), derived from the Schedule for Affective Disorders and Schizophrenia.[22] Depressive symptoms, as reported previously for the study group[20] were assessed using the 17-item Hamilton Depression Rating Scale.[23]

The current study utilized data from the first 6 months of the original 18-month study because it was felt that it would be difficult during a longer observation period to differentiate possible destabilizing effects of treatment from the natural course of illness. Manic or hypomanic symptoms reasonably attributable to treatment also, by definition, would involve study of effects during the first few months of continuation-phase therapy after randomization, rather than events during longer-term maintenance treatment.

All subjects provided verbal and written informed consent prior to participation in the study protocol, which was approved by the institutional review boards at each study site. The protocol was conducted at each site in accordance with the Declaration of Helsinki.

Operational Definitions of Mood Destabilization

Four events related to emergent manic/hypomanic symptoms were operationally defined during the randomized phase. The first of these utilized one of the original primary outcome points of the original trial,[14] namely, time until an intervention for a manic, hypomanic, or mixed episode. Achievement of this primary endpoint occurred based on the discretion of each subject's study physician. The 3 remaining mood elevation events were defined based on 3-tiered definitions of threshold MRS-11 scores: (1) ≥ 14, (2) ≥ 8, and (3) ≥ 4. Time to a given event was defined as time to reaching a given threshold, or intervention for a manic, hypomanic, or mixed episode, whichever occurred first. These severity thresholds were chosen by consensus among the authors, based on clinical observations in which scores of 14 of higher typically appear associated with syndromal mania, and scores of 8 to 13 reflect subsyndromal mania symptoms.[24] Although an MRS-11 score of 4 generally would be regarded as below a level of clinical significance, this cut-point was included as a lowest stratum because analysis of the raw data showed that for any given week, the MRS-11 standard deviation was about 4. Because most subjects (60%) had MRS-11 scores equal to 0 at randomization, the actual MRS-11 scores may be thought of as reflecting the change in MRS-11 from randomization.

Statistical Analyses

Median comparisons between 2 groups were analyzed by Wilcoxon tests. Dichotomous variables were examined using χ^2 tests. For both the open-label and randomized phases, risk for treatment-emergent manic/hypomanic symptoms was examined by multivariate time-to-event analyses using the Wei-Lin-Weissfeld method[25] with the full intent-to-treat sample. During the randomized phase, Kaplan-Meier survival analyses were also used to compare the probability of remaining event-free during the 6-month study period. Separate Cox models were fitted for each of the mood destabilization events controlling for relevant covariates. The Wei-Lin-Weissfeld method was applied to obtain weighted average hazard ratios across each of the mood-destabilization events. The study hypothesis involved demonstrating that the hazards ratio for lamotrigine versus placebo during the randomized phase was not meaningfully greater than 1.00, while controlling for other pertinent variables. We further sought to determine whether or not the upper bound of a 95% confidence interval for the weighted hazard ratio of lamotrigine versus placebo was meaningfully higher than 1.0.

During the randomized phase, 4 Cox proportional hazards models, referred to as component models, were fitted based on the 4 separate outcome events in an intent-to-treat fashion (ie, [1] time to intervention for manic/hypomanic/mixed symptoms, [2] MRS-11 score ≥ 4, [3] MRS-11 score ≥ 8, and [4] MRS-11 score ≥ 14). Each component model was adjusted for MRS-11 scores at randomization and screening; gender; age (categorized); and the occurrence of a manic, mixed, or hypomanic episode in the year preceding the study. The component models, in turn, were used to form a composite model via the Wei-Lin-Weissfeld method. This method uses the score residuals from each component model to account for the correlation between the multiple events for a given individual. The composite model produces a weighted average hazard ratio for each predictor in the model. The weighted hazard ratio for lamotrigine is interpreted as the multiplicative increase in hazards of any event for lamotrigine versus placebo, adjusting for gender, age, previous episode in past year, and MRS-11 scores at randomization and screening.

In fitting a Cox proportional hazards model, it was assumed that subjects who dropped out of the study without an intervention for a manic, hypomanic, or mixed episode did not drop out due to manic symptoms. It was also assumed that the hazard ratio for a given variable is proportional over time (eg, that the hazard ratio for lamotrigine versus placebo is constant over the 6 months of observation).

RESULTS

Mood Destabilization During Open-Label Phase

Among the 966 current or recently depressed bipolar subjects in the intent-to-treat sample, 93 (10%) had a rise in MRS-11 score of 14 points or more during the 8- to 16-week open-label lamotrigine titration phase, while 194 of

Table 1. Cox Proportional Hazard Model for Mood Destabilization Using the Wei-Lin-Weissfeld Method: Open-Label Phase of Lamotrigine Treatment in Current or Recently Depressed Bipolar Subjects (N = 966) Pre-Randomization

Parameter	Parameter Estimate[a]	SE	*P* Value	Hazard Ratio	95% CI Hazards Ratio
MRS-11 score at screen	0.015	0.016	.338	1.02	0.98 to 1.05
No. of past year manic/hypomanic/mixed episodes					
1–2 vs 0	0.305	0.154	.048	1.36	1.00 to 1.83
≥ 3 vs 0	0.702	0.204	.001	2.02	1.35 to 3.01
Male sex	0.100	0.108	.354	1.11	0.89 to 1.37
Age 30 to < 40 y	−0.213	0.168	.204	0.81	0.58 to 1.12
Age 40 to < 50 y	−0.138	0.150	.359	0.87	0.65 to 1.17
Age 50+ y	−0.328	0.165	.047	0.72	0.52 to 1.00

[a]Average increment/change in the log hazards ratio for either a one-unit increase in the explanatory variable (if continuous) or for a particular level of an explanatory variable versus the reference group (if categorical).
Abbreviation: MRS-11 = 11-item Mania Rating Scale.

Table 2. Numbers of Subjects With Manic/Hypomanic/Mixed Symptom Levels During the Randomized Phase After 6 Months of Treatment

	Placebo (n = 115)		Lamotrigine (n = 160)		Total (n = 275)	
Event	Count	%	Count	%	Count	%
Intervention	13	11	17	11	30	11
MRS-11 score ≥ 14	20	17	26	16	46	17
MRS-11 score ≥ 8	28	24	38	24	66	24
MRS-11 score ≥ 4	50	43	66	41	116	42

Abbreviation: MRS-11 = 11-item Mania Rating Scale.

the 966 (20%) had an MRS-11 score rise of at least 8 points, and 341 of 966 (35%) had an MRS-11 rise of 4 points or more from baseline. As shown in Table 1, a Cox regression model using the Wei-Lin-Weissfeld method for weighted average hazard ratios across these 3 outcome definitions revealed significant associations between MRS-11 rises and (1) having 1–2 manic/hypomanic/mixed episodes in the preceding year (hazard ratio = 1.36; $P = .048$), (2) having 3 or more manic/hypomanic/mixed episodes in the preceding year (hazard ratio = 2.02; $P = .001$), and (3) age greater than or equal to 50 years at the time of study entry (hazard ratio = 0.72; $P = .047$).

Mood Destabilization During Randomized Phase

Of the 463 patients at treatment randomization, 171 were randomly assigned to lamotrigine 200 or 400 mg/d (n = 124 and n = 47, respectively), and 121 were assigned to placebo, with the remainder (n = 171) randomly assigned to lithium. Subjects taking lamotrigine 50 mg/d were excluded from the analysis, as were subjects lacking an MRS-11 score at randomization or lacking at least 1 postrandomization efficacy assessment. After exclusions, there remained 160 patients taking lamotrigine 200 or 400 mg/d (n = 117 and n = 43, respectively) and 115 patients taking placebo. Of these 275 subjects, 60% had MRS-11 scores equal to 0 at baseline, and 85% had MRS-11 scores less than 4.

Table 2 presents the number of events by treatment for each of the events during the randomized phase. The counts for each MRS-11 event include subjects undergoing intervention for a manic, hypomanic, or mixed episode. The percentage of patients with an event is consistently similar between subjects taking lamotrigine or placebo.

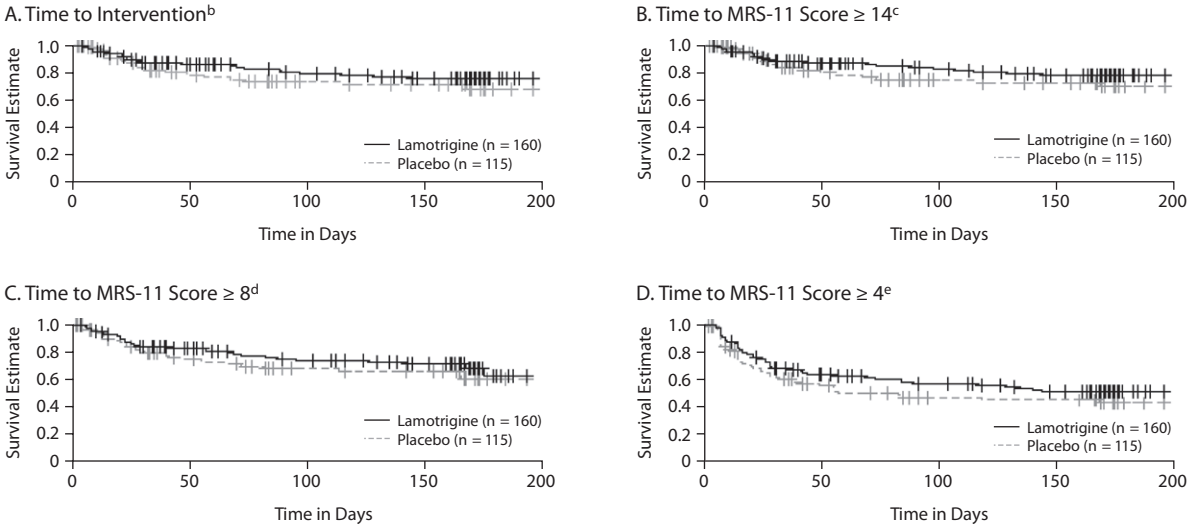
Kaplan-Meier survival curves shown in Figure 1 depict the estimated probability of survival for each event, for each treatment group across time, adjusting for no additional variables. The graphs show that subjects taking lamotrigine had consistently *higher* estimates of survival than those taking placebo across all 4 thresholds of mania.

Predictors of Mood Destabilization

In addition to demographic characteristics, 2 clinical covariates were chosen for inclusion in the Cox regression models for predicting mood destabilization events. First, manic symptom severity during open-label treatment as well as residual mania symptoms upon randomization were considered, based on data suggesting that the presence of subsyndromal manic or hypomanic symptoms may be predictive of relapse into more fulminant mania or hypomania.[24,26] Second, the number of manic, hypomanic, or mixed episodes in the preceding year was considered as a covariate based on prospective studies of individual-specific propensity to recurrence.[27] Initially, separate Cox proportional hazard models were calculated to screen the relationship between the number of past year manic, hypomanic, or mixed episodes and each of the 4 outcome events. Significant associations were found with this variable and (1) time to intervention for a manic/hypomanic/mixed episode (hazard ratio = 1.34; $P = .01$), (2) MRS-11 score ≥ 14 (hazard ratio = 1.37; $P = .02$), and (3) MRS-11 score ≥ 8 (hazard ratio = 1.29; $P = .03$) and near-significant with (4) MRS-11 score ≥ 4 (hazard ratio = 1.19; $P = .06$). The past year number of manic/hypomanic/mixed episodes appeared to be more categorical than continuous in nature, based on inspection of raw number of episodes: 58 subjects had none (21%), 127 had 1 episode (47%), 59 had 2 (22%), and 28 had 3 or more (10%). Therefore, this variable was categorized in subsequent analyses on the basis of none, 1 or 2, and 3 or more past year episodes.

Four separate Cox models were calculated to predict destabilization events at the aforementioned varying thresholds (ie, time to intervention for a manic/hypomanic/

Figure 1. Kaplan-Meier Survival Curves of Time Until Occurrence of Mood Destabilization Using 4 MRS-11 Severity Levels[a]



[a]Tick marks along lines represent censored observations.
[b]Kaplan-Meier survival estimates for time to intervention for a manic, hypomanic, or mixed episode by treatment group up to 6 months.
[c]Kaplan-Meier survival estimates for time to MRS-11 score greater than or equal to 14 by treatment group up to 6 months.
[d]Kaplan-Meier survival estimates for time to MRS-11 score greater than or equal to 8 by treatment group up to 6 months.
[e]Kaplan-Meier survival estimates for time to MRS-11 score greater than or equal to 4 by treatment group up to 6 months.
Abbreviation: MRS-11 = 11-item Mania Rating Scale.

Table 3. Cox Proportional Hazard Model for Mood Destabilization Using the Wei-Lin-Weissfeld Method: Randomized Phase (n = 275)

Parameter	Parameter Estimate[a]	SE	*P* Value	Hazard Ratio	95% CI Hazards Ratio
Lamotrigine	−0.23	0.20	.24	0.79	0.54 to 1.16
MRS-11 score at screen	0.11	0.02	< .0001	1.12	1.07 to 1.16
MRS-11 score at randomization	0.16	0.02	< .0001	1.17	1.12 to 1.22
No. of past year manic/hypomanic/mixed episodes					
1–2 vs 0	0.12	0.25	.64	1.12	0.69 to 1.82
≥ 3 vs 0	0.82	0.33	.01	2.26	1.19 to 4.30
Male sex	0.01	0.19	.97	1.01	0.69 to 1.47
Age 30 to < 40 y	0.43	0.31	.17	1.54	0.83 to 2.84
Age 40 to < 50 y	0.60	0.29	.04	1.82	1.03 to 3.23
Age 50+ y	0.44	0.29	.13	1.55	0.88 to 2.73

[a]Average increment/change in the log hazards ratio for either a one-unit increase in the explanatory variable (if continuous) or for a particular level of an explanatory variable versus the reference group (if categorical).
Abbreviation: MRS-11 = 11-item Mania Rating Scale.

mixed episode, MRS-11 score ≥ 14, MRS-11 score ≥ 8, and MRS-11 score ≥ 4), while controlling for age, gender, MRS-11 score at screening, MRS-11 score at randomization, and the number of manic, hypomanic, or mixed episodes in the preceding year. The resulting hazard ratios and corresponding confidence intervals for the treatment arm were consistently < 1.00 and were neither statistically significant nor near-significant. Thus, for time to intervention, the hazard ratio for lamotrigine versus placebo was 0.83 (95% CI, 0.38 to 1.80; $P = .64$); for switch events defined by MRS-11 score ≥ 14, the hazard ratio was 0.79 (95% CI, 0.43 to 1.48; $P = .47$); for switch events defined by MRS-11 score ≥ 8, the hazard ratio was 0.86 (95% CI, 0.51 to 1.46; $P = .58$); and for switch events defined by MRS-11 score ≥ 4, the hazard ratio was 0.79 (95% CI, 0.54 to 1.16; $P = .24$). Confidence intervals are wider for the more extreme events due to the smaller number of subjects satisfying the criteria for these events. The fact that the hazard ratios for lamotrigine and placebo are all similar in direction and magnitude permit averaging across the component models using the Wei-Lin-Weissfeld method.

As shown in Table 3, the Wei-Lin-Weissfeld composite model estimate indicated that the estimated hazard of reaching an event for subjects randomly assigned to lamotrigine was 79% of the hazard for those taking placebo, adjusting for gender, age, past year manic/hypomanic/mixed episodes, and MRS-11 scores at screening and at randomization. The estimate was not statistically different from placebo at an α level of .05, with a directionality favoring *against* (rather than *for*) the occurrence of a mood

destabilization event. The upper limit of the 95% confidence interval (1.16), from a clinical standpoint, is not meaningfully greater than 1.00.

An increased hazard for mood destabilization was seen in subjects between ages 40 and 49. In addition, higher MRS-11 scores at screening and at randomization were significantly associated with higher hazards of a destabilization event at the $\alpha = .05$ level (P values $< .0001$). For every 1-unit increase in MRS-11 score at screening, the estimated hazards of an event increased by a factor of 1.12 (95% CI, 1.07 to 1.16). For every 1-unit increase in MRS-11 scores at randomization, the estimated hazard multiplies by 1.17 (95% CI, 1.12 to 1.23). Because most subjects had MRS-11 scores equal to 0 at randomization and screening, these significant estimates are largely driven by the few subjects with extreme MRS-11 scores at screening or randomization.

The presence of 3 or more manic, hypomanic, or mixed episodes in the preceding year also was significantly associated with an approximate 2-fold increased risk for destabilization events in the final composite Cox model. In addition, there was no significant interaction effect between treatment arm and a history of previous manic/hypomanic episodes, indicating that previous manic episodes were associated with rises in MRS-11 scores independent of treatment. Collectively, these findings suggest that during maintenance treatment for bipolar disorder, the likelihood of emergent manic or hypomanic features appears driven more by the pre-existing or historical burden of mania features, rather than the use of lamotrigine.

Quartile Analyses

As a final consideration, we identified subjects during the randomized phase who experienced a rise in MRS-11 scores from baseline ($n = 147$), which included 32 (22%) in the lowest quartile (maximum rise of 1) and 36 (24%) for the uppermost quartile (maximum rise of ≥ 9). Using a Wilcoxon 2-sample test to compare the medians of covariates across the 2 treatment arms, none of the covariates examined in the Cox models (ie, age, MRS-11 score at screening, MRS-11 score at randomization, or number of manic/hypomanic episodes in the preceding year) were significant or near-significant (all P values $\geq .20$). Additionally, χ^2 tests revealed no significant or near-significant differences between upper and lower quartile groups in gender or treatment arm.

DISCUSSION

Across several threshold severity levels of mania, the present findings found no evidence for a higher hazard for relapsing mania symptoms with lamotrigine than placebo during continuation phase maintenance pharmacotherapy in bipolar I disorder. The observed upper bound of a 95% confidence interval (1.16) suggests that, at most, the true hazard of lamotrigine triggering a clinically meaningful threshold for mood destabilization is no larger than 1.16-fold, which, for practical purposes, is not substantially different from 1.00. More striking, however, was the observed highly significant associations between the emergence of manic or hypomanic features during either the open-label or randomized phase and multiple past year manic/hypomanic/mixed episodes, as well as residual mania symptoms at randomization predicting subsequent rises in mania symptom severity during the randomized phase, independent of treatment arm. These latter findings are consistent with observations by Quitkin and colleagues,[28] suggesting that some patients with bipolar disorder may be more prone toward manias than depressions. Hence, at least in some instances, apparent mood destabilization may in fact reflect patient-specific factors (notably, lifetime mania illness burden and possibly older age as observed during the open-label phase) or possible lack of acute antimanic efficacy with lamotrigine, rather than adverse iatrogenic effects.

It is noteworthy that the vast majority of subjects (85%) had MRS-11 scores < 4 at the time of randomization, yet it is possible that even very low-grade, subsyndromal symptoms of mania could predispose recently depressed bipolar patients to the development of more fulminant manic symptoms.[24,26] This finding is consistent with observations during adjunctive antidepressant pharmacotherapy for bipolar depression in the National Institute of Mental Health Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD),[29] as well as findings from the Bipolar Collaborative Network (formerly the Stanley Foundation Bipolar Network) recently reported by Frye et al.[30]

Prior observations suggest that while lamotrigine exerts prophylactic efficacy against either manic or depressive occurrences, its effect appears more robust against depression than mania. Such findings complement those reported elsewhere for lithium during maintenance pharmacotherapy of bipolar disorder, inasmuch as bimodal efficacy is evident overall, but appears more dramatic for the prevention of mania than depression.[31] Refined concepts about mood stabilizing agents have increasingly drawn distinctions between the extent to which a compound can achieve and sustain euthymia by virtue of a predominant antimanic versus antidepressant effect,[2] in tandem with its ability not to induce the opposite polarity of illness.

A number of limitations warrant consideration when interpreting the current findings. The operational definitions of mood destabilization used in the present study were based on MRS-11 scores rated at each study visit, although the original study protocol was designed using a primary outcome measure of time to intervention for any mood episode. Moreover, generalizations about mood destabilization as a phenomenon are limited by the present comparison of lamotrigine or placebo after acute stabilization with lamotrigine from an index depressed-phase episode. It is possible that other factors not captured within the present study might influence destabilization during continuation

phase therapy, such as cotherapy with agents possessing acute antimanic efficacy,[32] or outcome with long-term use of antidepressants. The study protocol also did not allow consideration for patient-specific factors that may increase propensity for antidepressant-induced mania, such as recent substance abuse[33,34] (excluded from study enrollment) or past antidepressant-induced manias[35] (not assessed); such factors also may not bear equally on affective polarity switches related to nonantidepressants (eg, anticonvulsants, atypical antipsychotics), or to switch events that arise in the acute versus postacute/continuation phase of treatment. However, a combined analysis of 5 acute (7–10 week duration) randomized monotherapy studies comparing lamotrigine versus placebo for bipolar depression identified formal polarity switches from depression to mania, hypomania, or mixed episodes in similar proportions of subjects taking lamotrigine (20/531 [3.8%]) or placebo (17/515 [3.3%]).[36]

The consistent directionality of our nonsignificant findings raises the possibility that limited sample size may have yielded insufficient statistical power to detect a modest *decrease* in the hazard ratio for emergence of manic symptoms with lamotrigine compared to placebo. Such observations are consistent with previously published survival analyses demonstrating longer time until intervention for an emerging manic episode with lamotrigine than placebo in a pooled analysis of two 18-month maintenance trials,[15] a finding not evident with the smaller sample sizes of each individual trial considered independently. Finally, it is theoretically possible that cessation of lamotrigine after the open-label phase could have led to an increased rate of mania relapses among subjects subsequently randomized to placebo—a critique relevant to all long-term studies that randomly assign subjects to active drug or placebo following an open-label phase—although we are aware of no evidence to suggest higher or faster rates of affective relapse following abrupt versus gradual cessation of lamotrigine.

In summary, the present findings support the utility of an operational definition for mood destabilization during maintenance treatment for bipolar I disorder based on a composite of mania symptom severities at varying thresholds. Based on data from the first 6 months of an 18-month randomized comparison of lamotrigine or placebo, as well as data during open-label titration of lamotrigine, this applied definition suggested no statistically or clinically meaningful increased likelihood for treatment-associated mood destabilization. However, the present findings are consistent with prior reports pointing to residual mania symptoms and illness burden related to prior manic episodes as risk factors for mood destabilization during maintenance pharmacotherapy for bipolar I disorder.

Drug names: aripiprazole (Abilify), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa).

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