Lamotrigine in Rapid-Cycling Bipolar Disorder

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Background: We evaluated the antidepressant and mood-stabilizing effects of lamotrigine, a novel anticonvulsant, in a group of rapid-cycling bipolar patients. Most were already nonresponders or poor partial responders to other conventional mood-stabilizing agents.

Method: This open, naturalistic, and prospective study was conducted with five rapid-cycling bipolar patients (DSM-IV). Each received lamotrigine titrated to a minimum dose of 150 mg/day as monotherapy or in combination with other psychotropic agents. Patients were assessed with the Global Assessment Scale (GAS), Beck Depression Inventory (BDI), and Young Mania Rating Scale (YMRS) for evidence of cycling mood.

Results: Lamotrigine was used at a mean ± SD dose of 185.0 ± 33.5 mg/day for 225.8 ± 28.0 days. Random regression modeling of data showed significant dose- and time-dependent improvements in depressive symptoms and social function of patients taking lamotrigine (Dose: $z = 2.17$, $p < .03$ for BDI, $z = 4.44$, $p < .001$ for GAS; Time: $z = –3.79$, $p < .001$ for BDI, $z = 2.16$, $p < .03$ for GAS). Further random regression modeling analysis of change over time in symptoms prior to lamotrigine compared with symptoms during lamotrigine treatment showed a significant treatment by time effect for GAS ($z = 2.40$, $p < .016$) and a trend for BDI scores ($z = –1.79$, $p < .073$). No significant time or dosage effect or time by treatment effect was observed for YMRS. Finally, t statistics showed a significant reduction in mean BDI scores following treatment with lamotrigine ($t = –5.26$, $p < .006$). Lamotrigine was well tolerated by all patients; only one patient experienced several side effects, which were probably due to interaction between several psychotropic medications.

Conclusion: Lamotrigine augmentation therapy and monotherapy appeared to have mood-stabilizing and antidepressant efficacy in the treatment of five rapid-cycling bipolar patients. The effect persisted for an average of 7.5 months.

(J Clin Psychiatry 1997;58:522–527)

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The authors gratefully acknowledge the secretarial assistance of Ms. Janet Bockenstedt.

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Rapid-cycling bipolar disorder affects 13% to 20% of all bipolar patients, and 72% to 82% of these patients are resistant to lithium therapy.[1] This variant of bipolar disorder is associated with greater morbidity such as substance abuse, anxiety disorders, borderline personality disorder, and hypothyroidism.[1,2] Patients also suffer a higher rate of mortality by suicide.[3] Alternative therapeutic agents are needed for this population since the currently available mood stabilizers can be ineffective or inadequate at relieving the depressive component of mood cycles.[4] An additional concern is that the use of antidepressants in bipolar patients has been associated with the induction of mania and the development of rapid cycling,[5] which often precludes their use on a continued basis.

Recently, we reported on the antidepressant effects of lamotrigine in a patient with rapid-cycling bipolar I disorder.[6] In the current preliminary study, we have extended our observations to a similar group of five rapid-cycling bipolar patients. All patients exhibited greater mood-stabilizing as well as significant antidepressant effect for periods of treatment ranging from 189 to 265 days. To our knowledge, this is the first report of lamotrigine's mood-stabilizing and antidepressant effects in a population of treatment-resistant rapid-cycling bipolar patients.

METHOD

All patients referred to the Mood Disorders Program at Case Western Reserve University and University Hospitals of Cleveland, Ohio, between February 1990 and February 1997 who were diagnosed with rapid-cycling bipolar I and II disorders were eligible for the study. Patients were diagnosed by one of us (D.J.R.) using a systematic

Table 1. Demographic and Clinical Data for Patients on Lamotrigine Treatment*

Patient	Age (y)	Sex	Diagnosis and Duration	Comorbid Diagnoses	Concurrent Medications	Total Treatment Time (d)	Duration of Treatment With Other Agents (d)	Duration of Treatment With Lamotrigine (d)	Duration of Monotherapy With Lamotrigine (d)	Final Dose of Lamotrigine (mg)
1	43	F	BPI, mixed RC 3 y		Fluoxetine	305	40	265	190	225
2	27	F	BPII, RC 14 y		Divalproex	1502	1290	212	107	200
3	40	F	BPII, depressed RC 20 y	Personality disorder NOS	Divalproex	803	571	232	90	200
4	37	F	BPII, RC, depressed 20 y	Borderline PD, hypothyroidism	Divalproex, lithium, tetraiodothyronine, triiodothyronine	1677	1446	231	0	150
5	48	F	BPII, RC 20 y	Panic disorder, borderline PD, hypothyroidism	Divalproex, triiodothyronine, fluoxetine, methylphenidate	1291	1102	189	43	150
Total (mean ± SD)	39 ± 7.8					1115.6 ± 559.0	889.8 ± 578.4	225.8 ± 28.0	86 ± 71.6	185.0 ± 33.5

*Abbreviations: BPI = bipolar I, BPII = bipolar II, PD = personality disorder, RC = rapid cycler.

computerized checklist of the DSM-IV criteria.[7] Patients with active drug or alcohol abuse or serious medical problems were excluded from this study. The method of the study was open, naturalistic, and prospective.

In all cases, informed verbal and written consent was obtained after the procedure had been fully explained to each patient. Patients were monitored for symptoms of depression, mania/hypomania, and side effects every 4 to 6 weeks. Beck Depression Inventory (BDI),[8] Young Mania Rating Scale (YMRS),[9] and Global Assessment Scale (GAS)[10] scores were obtained during all visits by one rater (D.J.R.). The dose of lamotrigine was initiated and titrated to a minimum dose of 150 mg/day according to the FDA-approved protocol[11] and previously reported.[6]

Patients initially received lamotrigine in conjunction with other agents including fluoxetine, methylphenidate, divalproex sodium, triiodothyronine, tetraiodothyronine, and lithium.

Statistical Analysis

Random regression models were computed to evaluate change in BDI, GAS, and YMRS scores as a function of time and treatment dose with lamotrigine. Dose was modeled as a lagged variable, with dosage prescribed at one date predicting symptoms at the next measurement interval. Additional analyses were conducted to compare symptom change over time before and after administration of lamotrigine.

In a random regression model,[12,13] change over time is modeled at both the individual and population levels. Individual models of change over time are estimated and augmented using population-level trend data. This type of model offers some unique advantages over mixed-effects ANOVA models, which allow for random responses of individuals over time but are restricted to modeling time as a fixed effect. In random regression models, time can also be modeled as a random factor, and, thus, each individual can vary in both the number of measurements over time and the time course of those measurements. Furthermore, mixed-effects ANOVA models allow no missing data. Random regression models are based on an individual's available data for each point, but augment from population data using empirical Bayes' estimation methods when individual level data are missing. Thus, all available data can be used in the estimation of change. The MIXREG[14] random regression program was used to fit the models.

RESULTS

Five women ranging in age from 27 to 48 years entered the study. Their duration of treatment before lamotrigine ranged from 40 to 1446 days, with a mean of 889.8 days (Table 1). The patients had suffered from bipolar I or II disorder with rapid cycling for a period of 3 to 20 years and were generally nonresponders or partial responders to other mood stabilizers. Three of the patients also carried other diagnoses such as borderline personality disorder (Patients 4 and 5), personality disorder NOS (Patient 3), panic disorder (Patient 5), and hypothyroidism (Patients 4 and 5) (Table 1). Duration of lamotrigine treatment ranged from 189 to 265 days with a mean of 225.8 days (Table 1). The mean dose of lamotrigine was 185 mg/day (Table 1). Four of the patients were successfully tapered off all other medications other than thyroid supplements. One patient continued to be treated with a combination of lithium, divalproex sodium, and lamotrigine (Table 1). Comparison of behavioral scores before and after treatment with lamo-

Table 2. BDI, GAS, and YMRS Scores Before and After Treatment With Lamotrigine*

	BDI[a]				GAS[b]				YMRS[c]			
	Before		After		Before		After		Before		After	
Patient	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
1	17.33	12.1	6.17	2.9	61.67	2.9	74.50	4.6	6.67	5.7	1.17	2.0
2	13.87	14.2	4.50	3.6	66.24	13.7	81.67	7.5	0.24	1.2	1.50	3.7
3	12.11	6.6	6.00	6.4	73.89	9.3	79.00	8.2	0	0	0	0
4	11.58	8.6	8.75	6.5	64.96	7.3	52.47	9.2	0.13	0.7	0.47	0.8
5	19.57	10.6	11.25	5.0	66.63	9.8	76.00	1.7	0	0	0	0
Total mean	14.89	3.4	7.33	2.66	66.67	4.5	72.90	11.7	1.40	2.9	0.67	0.7

*Abbreviations: BDI = Beck Depression Inventory, GAS = Global Assessment Scale, YMRS = Young Mania Rating Scale.
Comparison of before vs after lamotrigine treatment scores: [a]BDI: t = –5.260, p < .006; [b]GAS: t = –1.223, p < .289; [c]YMRS: t = –0.649, p < .552.

trigine (Table 2) showed improvements in all scores; however, only the mean BDI score dropped significantly after treatment with lamotrigine (t ≅ –5.260, p < .006, Table 2).

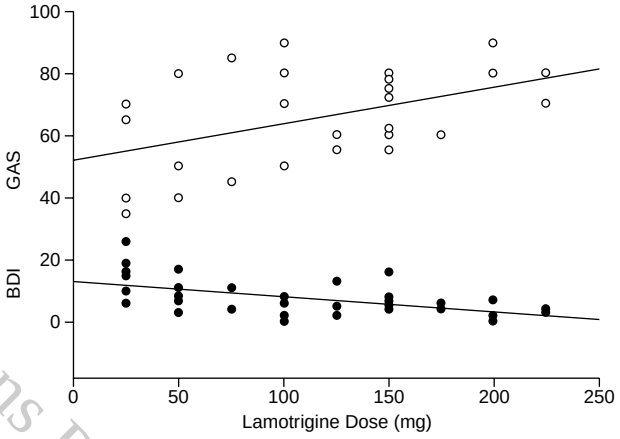
Random regression models examined change in symptoms over time during treatment with lamotrigine. It was found that BDI symptoms declined significantly over time (z = –3.79, p < .001) and GAS scores increased significantly over time (z = 2.16, p < .031) (Figure 1). A second set of models were then run in which change over time competed with change as response to dose. In these models, BDI symptoms no longer showed a significant time effect but did reveal a significant dose effect (z = 2.17, p < .030). There was a decrease of 4.1 symptoms for every 100 mg of lamotrigine administered. Similarly, for GAS, time was no longer a significant predictor, but there was a significant dose response (z = 4.44, p < .001). For every 100 mg of lamotrigine administered, there was a 10.5-point increase in GAS score (Figure 1). No significant time or dosage effects were observed for symptoms on the YMRS.

Further random regression models examined change over time in symptoms before lamotrigine compared with symptoms during lamotrigine treatment. Total treatment time before lamotrigine ranged from 40 to 1446 days with a mean of 889.8 days. A significant treatment by time effect was observed for GAS scores (z = 2.40, p < .016). Improvement was 0.8 points per 100 days before lamotrigine (Figure 2) and 5.59 points per 100 days during lamotrigine treatment. A trend was also found when comparing change in BDI symptoms over time before and after treatment with lamotrigine (z = –1.79, p < .073). Before lamotrigine, BDI symptoms showed essentially no change, actually increasing 0.09 points per 100 days of treatment. Under lamotrigine, BDI scores decreased 3.9 points per 100 days of treatment. There was no significant time by treatment condition interaction for YMRS scores over the course of treatment before or after lamotrigine.

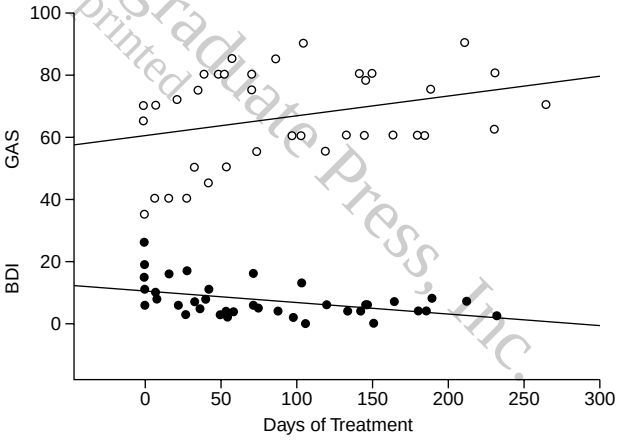
Illustrative Cases

The following case vignettes demonstrate the symptoms present in this patient group before and after lamotrigine treatment.

Figure 1. Individual BDI and GAS Scores Versus Lamotrigine Doses and Times of Treatment*



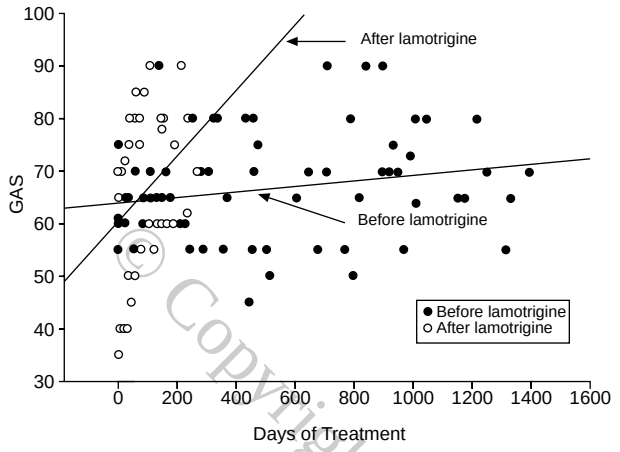
BDI vs Dose: intercept = 13.20, slope = –0.050, r^2 = .30.
GAS vs Dose: intercept = 51.96, slope = 0.116, r^2 = .22.



BDI vs Days of Treatment: intercept = 10.69, slope = –0.039, r^2 = .22.
GAS vs Days of Treatment: intercept = 60.24, slope = 0.063, r^2 = .098

*Abbreviations: BDI = Beck Depression Inventory, GAS = Global Assessment Scale. Regression lines seen here are for descriptive purposes. Moreover, slopes and intercepts reported here are based on multiple data points from the same individuals and thus are estimates. See text for slopes and intercepts derived from the mixed regression analysis.

Figure 2. Impact of Lamotrigine on Global Assessment Scale (GAS) Scores During Days of Treatment



Case 1. A 43-year-old white woman with a 3-year history of bipolar I disorder, mixed, rapid-cycling subtype, presented in a mixed state. She had been taking fluoxetine 20 mg for over 1 year and presented because of persistently dysphoric mood. She was given the option to add lamotrigine to her regimen or a conventional mood stabilizer and elected lamotrigine therapy. Lamotrigine was initiated using the standard protocol. Within 1 month, she reported that her mood was significantly less sad, less irritable, and less dysphoric on the combination of lamotrigine 150 mg and fluoxetine 20 mg per day. After another month, the fluoxetine was tapered to 10 mg. After 8½ weeks of combination therapy, she reported episodes of irritability that were more mild and being "calmer and more relaxed," with cessation of crying spells and racing thoughts. Two weeks later, fluoxetine therapy was discontinued, and lamotrigine was empirically increased to 225 mg/day. Her mood assessed 11 weeks after starting treatment was determined to be euthymic.

Case 2. A 27-year-old white woman with a 14-year history of bipolar II disorder, rapid-cycling subtype, presented to our clinic in 1992. Treatment with divalproex sodium was instituted at therapeutic levels, but, despite treatment, she continued to suffer major mood swings. Between 1992 and the initiation of lamotrigine in mid-1995, she suffered six episodes of recurrent major depression and four episodes of unequivocal hypomania; each episode occurring while she was taking therapeutic levels of divalproex sodium sometimes in combination with antidepressants. In mid-1995, she failed to respond to a combination of divalproex sodium and carbamazepine because of intolerable side effects. Following this and during a brief euthymic interval, lamotrigine was started per the standard protocol and added to divalproex sodium 1500 mg/day. At the outset, our intention was to titrate lamotrigine empirically to a dose of 150 mg, and, once a clinical response was evident, to taper her off of the divalproex sodium. Over the next 3 months, divalproex sodium was discontinued, and lamotrigine 200 mg/day was achieved. Since the completion of lamotrigine titration, her mood has been maintained, cycle free for the period of this study.

Case 3. A 40-year-old white woman with a 20-year history of bipolar II disorder, rapid-cycling subtype and personality disorder NOS presented in the depressed phase of her illness to our clinic. She was initially treated with divalproex sodium monotherapy for 4 months until, because of persistent depression, sertraline was added. She remained on the combination of sertraline 100 mg/day and divalproex sodium (low blood levels of approximately 40 ng/L) for the next 11 months. Sertraline was discontinued because of persistently lowered libido. Over the next 5 months, she remained on divalproex sodium monotherapy but failed to tolerate this because of recurrent depression. At that time, lamotrigine therapy was offered and accepted. A combination of lamotrigine and divalproex sodium were used initially per the standard protocol. Her dosage of divalproex sodium remained unchanged initially, but, within 4 months, it was tapered and discontinued. Thereafter, she has remained on lamotrigine monotherapy with good effect. At the last evaluation, she described her mood swings as significantly more mild, lasting approximately 3 days and still occurring approximately every 2 weeks. She is no longer functionally impaired by her cycling.

Case 4. A 37-year-old white woman with a 20-year history of bipolar II disorder, rapid-cycling subtype, had comorbid borderline personality disorder and hypothyroidism. Despite adequate treatment at therapeutic levels of lithium and divalproex sodium for 5 years, she suffered one episode of hypomania and two distinct episodes of recurrent depression 2 years apart, just prior to the introduction of lamotrigine therapy. She was offered lamotrigine as a possible therapeutic agent to be combined with her current doses of lithium and divalproex sodium with the hope that it would reduce or eliminate her recurrent mood swings. Lamotrigine was added according to the standard protocol in September 1995 and titrated empirically to 150 mg/day. The result has been a marked diminution of her affective instability and recurrent mood swings. She feels that her mood is euthymic except during the week prior to her menstrual flow. At that time, she still becomes much more melancholic and irritable. Once her period starts, she feels euthymic again and otherwise has no complaints. She continues to tolerate the medications well with just a minor tremor.

Case 5. A 48-year-old white woman with a greater-than-20-year history of bipolar II disorder, rapid-cycling subtype had comorbid panic disorder without agoraphobia and borderline personality disorder. She also suffered

from hypothyroidism for which she was being adequately supplemented. This patient was treatment responsive to low doses of divalproex sodium at consistent blood levels of 36 ng/L, in combination with triiodothyronine, methylphenidate, and fluoxetine up to 60 mg/day. However, she was unable to tolerate this combination of medications due to excessive weight gain of greater than 40 lb (> 18.2 kg). After achieving a 16-week euthymic interval, she was offered lamotrigine, which was added to her regimen per the standard protocol. In 2 months, the dose of lamotrigine was titrated empirically to 100 mg/day, at which point divalproex was tapered and discontinued over a 4-week period. Lamotrigine was then titrated to 150 mg/day. Because her mood remained stable over the next 4 months, fluoxetine and methylphenidate were tapered and discontinued. Since then, her mood has remained clinically euthymic on lamotrigine monotherapy.

DISCUSSION

This study provides preliminary evidence that lamotrigine may be a safe and effective treatment for patients with treatment-resistant rapid-cycling bipolar disorder. Data collected so far suggest that lamotrigine is an effective antidepressant with potential to improve social functioning.

A strength of this study is the analysis of cumulative data on each patient extending from 305 to 1677 days using random regression models. These models take into account the considerable heterogeneity in the response of individuals to treatment. Moreover, random regression models allow for the presence of missing data, time-varying covariates, and subjects measured at different time points.[12–14]

Using random regression models, we were able to derive several important findings concerning the effect of lamotrigine in treatment of five rapid-cycling bipolar patients. Lamotrigine either alone or in combination with other agents caused significant time-dependent increases in GAS scores compared with treatment prior to lamotrigine, thus contributing to the overall improvement in social functioning of these patients.

A similar time-dependent trend was also seen when BDI scores were analyzed for a lamotrigine effect, indicating improvement in depressive symptoms. When mean BDI scores before and after treatment were investigated and analyzed, a significant lamotrigine effect could also be demonstrated. Finally, random regression models showed significant dose- and time-dependent improvements in social functioning and depression scales.

Another strength of this study concerns the use of lamotrigine in a population of rapid-cycling patients who generally were nonresponders or poor responders to lithium, divalproex, and carbamazepine and were considered treatment refractory. Indeed, four of five patients who participated in this study had long histories of bipolar disorder (14–20 years) and exhibited partial response or no response to various mood stabilizers and other agents. Addition of lamotrigine to their regimens decreased the frequency of cycling and improved their mood and social functioning.

The limitations of our study included the open nature of this trial, i.e., no control group, and the small number of subjects. Furthermore, all subjects in this study consisted of female patients, and thus our data may not be extrapolated to male patients with bipolar disorder.

Additionally, we cannot rule out the potential synergistic and mood-stabilizing effects of other agents taken by patients during this trial. Another limitation of this study relates to the ascertainment of diagnoses based on clinical interview and use of a systematic computerized checklist of DSM-IV criteria and not a structured diagnostic instrument.

The current preliminary report extends our previous case report[6] demonstrating the potential antidepressant effects of lamotrigine in a rapid-cycling bipolar patient. This report is the first report of a group of bipolar patients with rapid cycling who have responded favorably to the addition of lamotrigine for an average of 7.5 months. All patients tolerated the addition of lamotrigine. Only one patient while taking lithium and divalproex sodium concurrently experienced side effects including nausea, headache, dizziness, dry mouth, constipation, loose stools, rash, and tremor. Despite potential benefits of lamotrigine, the results of this study should be interpreted cautiously due to the open design of the study, small sample size, and use of concurrent psychotropic medications early during the initiation of the trial with lamotrigine. The study does show, however, the promise of a new mood-stabilizing agent that works through a novel mechanism of action by stabilizing presynaptic neural membranes, thereby modulating release of excitatory amino acids. Currently, a multicenter, placebo-controlled, fixed-dose study of the safety and efficacy of lamotrigine in the treatment of bipolar disorder is ongoing.[15]

Drug names: carbamazepine (Tegretol and others), divalproex sodium (Depakote), fluoxetine (Prozac), lamotrigine (Lamictal), methylphenidate (Ritalin), sertraline (Zoloft).

REFERENCES

1. Calabrese JR, Fatemi SH, Kujawa MJ, et al. Predictors of response to mood stabilizers. J Clin Psychopharmacol 1996;16:24S–31S
2. Bauer MS, Calabrese JR, Dunner DL, et al. Multi-site data reanalysis: validity of rapid cycling as a course modifier for bipolar disorder in DSM-IV. Am J Psychiatry 1994;151:506–515
3. Fawcett J, Scheftner W, Fogg L, et al. Time-related predictors of suicide in major affective disorder. Am J Psychiatry 1990;147:1189–1194
4. Okuma T. Effects of carbamazepine and lithium on affective disorders. Neuropsychobiology 1993;27:138–145
5. Altshuler LL, Post RM, Leverich GS, et al. Antidepressant-induced mania and cycle acceleration: a controversy revisited. Am J Psychiatry 1995; 152:1130–1138
6. Calabrese JR, Fatemi SH, Woyshville MJ. Antidepressant effects of la-

motrigine in rapid cycling bipolar disorder [letter]. Am J Psychiatry 1996; 153:1236
7 . American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994:317–391
8. Beck AT, Ward CH, Mendelson M, et al. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561–571
9. Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry 1978;133:429–435
10. 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
11. Lamictal (lamotrigine). Physicians' Desk Reference. Montvale, NJ: Medical Economics; 1997:1105–1110
12. Gibbons RD, Hedeker D, Watermaux C, et al. Random regression models: a comprehensive approach to the analysis of longitudinal psychiatric data. Psychopharmacol Bull 1988;24:438–443
13. Gibbons RD, Hedeker D, Elkin I, et al. Some conceptual and statistical issues in analysis of longitudinal psychiatric data. Arch Gen Psychiatry 1993;50:739–750
14. Hedeker D. MIXREG: a FORTRAN Program for Mixed-Effects Linear Regression Models. Chicago, Ill: Prevention Research Center, University of Illinois; 1993
15. Calabrese JR, Bowden CL, McElroy S, et al. Efficacy of lamotrigine in bipolar disorders: preliminary data on affective disorders. In: Manji HK, Bowden C, Belmaker R, eds. Mechanisms of Antibipolar Disorder Treatments: Focus on Lithium, Valproate, and Carbamazepine. Washington, DC: American Psychiatric Press; 1997