Effect of Open-Label Lamotrigine as Monotherapy and Adjunctive Therapy on the Self-Assessed Cognitive Function Scores of Patients With Bipolar I Disorder

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Abstract: Cognitive deficits in patients with bipolar disorder are likely to impair occupational and social functioning. In a post hoc analysis of data from a prospective, open-label study of lamotrigine in 1175 patients 13 years or older with bipolar I disorder, changes in the self-rated cognitive function scores of patients receiving lamotrigine as monotherapy or as adjunctive therapy were evaluated. Lamotrigine was given for 12 weeks, with a target dosage of 200 mg/d. Cognitive function was assessed at baseline and week 12 with the self-rated Medical Outcomes Study Cognitive (MOS-Cog) Scale. Mean MOS-Cog scores improved significantly from baseline in the overall group (+8.4 ± 22.55 points, $P < 0.0001$) and in subgroups of patients receiving and not receiving concomitant valproate, antidepressants, or antipsychotics. Patients receiving lamotrigine and not receiving concomitant antipsychotics, however, exhibited a small but significantly greater degree of improvement than patients who were receiving concomitant antipsychotics (adjusted mean difference = 4.05; 95% confidence interval, 1.30–6.81; $P = 0.0039$). Statistically significant improvement was seen in patient subgroups with a depressive (mean change from baseline, 8.8 ± 21.97; $P < 0.0001$) or a manic (mean change from baseline, 7.5 ± 22.62; $P = 0.0007$) index episode. Improvements in MOS-Cog scores significantly correlated with improvement in both depressive (correlation coefficient, −0.339; $P < 0.0001$) and manic (correlation coefficient, −0.151; $P < 0.0001$) symptoms. Overall, self-rated cognitive function scores improved during open-label lamotrigine therapy in patients with bipolar I disorder whether or not they were receiving concomitant valproate, antidepressants, or antipsychotics. Additional research is needed to explore the clinical relevance of these findings.

(*J Clin Psychopharmacol* 2007;27:387–391)

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Received October 10, 2006; accepted after revision April 9, 2007.

This study was supported by GlaxoSmithKline.

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ISSN: 0271-0749/07/2704-0387

DOI: 10.1097/JCP.0b013e3180a76dd2

It has been suggested that behavioral and pharmacological therapies for cognitive impairment may improve functional outcomes in patients with bipolar disorder.[1,2] This suggestion is based on the observations that the extent of specific cognitive impairments, for example, deficits in sustained concentration, executive functioning, episodic memory, and visuospatial skills, is correlated with the number and severity of mood episodes (mania or depression) and that cognitive function, in particular, memory, may predict the employment status and psychosocial functioning of patients with bipolar disorder.[1,3,4]

Lamotrigine, approved in 2003 for the maintenance treatment of bipolar I disorder, appears to have a favorable cognitive profile. Lamotrigine does not impair cognitive function as determined by objective neuropsychological measures and subjective reports[5–9] and may have a beneficial effect on cognitive activation and alertness as determined by time-reaction measurements in healthy volunteers.[5] No published studies have used neuropsychological tests to assess the effects of lamotrigine on cognitive function in patients with bipolar disorder, although in patients with epilepsy, lamotrigine does not appear to impair neuropsychological test performance,[10–12] although a small study reported a slight reduction in information processing speed.[10] In a report of 5 elderly patients with age-associated memory impairment, lamotrigine improved immediate and delayed visual memory as well as delayed logical memory.[13]

Patients with bipolar disorder are commonly treated with more than 1 medication,[14,15] and it is therefore important to recognize the cognitive effects of possible concomitant medications. Valproate has been shown to impair cognitive function in healthy adults,[16] but its cognitive effects have not been systematically evaluated in patients with bipolar disorder. Antipsychotic agents with anticholinergic activity, including olanzapine and quetiapine, have been associated with cognitive decline in elderly patients with dementia.[17,18] Tricyclic antidepressants may produce memory impairment as a result of their anticholinergic activity,[19] and varying cognitive effects of selective serotonin reuptake inhibitors have been reported.[20,21]

In 2 open-label clinical trials, Khan et al[22] found a similar and statistically significant improvement from baseline in self-rated cognitive function scores among recently manic (n = 349) or depressed (n = 966) patients with bipolar I function at the end of 8- to 16- week open stabilization phases after therapy with lamotrigine (100–200mg/d) as

monotherapy or adjunctive therapy. Improvement in cognitive scores was greater in patients with baseline depression than in those with baseline mania.

In the current post hoc analysis of data from a recent open-label study with lamotrigine, which included a large sample of patients with bipolar I disorder,[23] we evaluated patients' self-rated cognitive scores during 12 weeks of treatment. Because it is important to evaluate cognitive effects in patients with bipolar disorder within the context of the other medications with which they often may be treated, the analysis also evaluated the impact of lamotrigine by subgroups based on the presence or absence of various concomitant medications. Finally, because cognitive impairment may be more common in elderly patients with bipolar disorder than in younger patients,[24] self-rated cognition in patients 65 years and older was separately examined.

MATERIALS AND METHODS

Institutional review board approval for this US multicenter study (GlaxoSmithKline protocol SCA40917) was obtained for each of the 188 study sites, and patients provided written informed consent before entering the study.

Patients

Eligible patients were male or female, 13 years or older, with a diagnosis, based on an unstructured clinical interview and a review of available medical records, of bipolar I disorder according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Patients currently being treated for bipolar disorder were required to have been treated with a stable regimen of psychotropic medications for at least the previous 2 months and not to have received lamotrigine before entering the study. Patients with confounding medical conditions or severe psychiatric symptoms that could interfere with study participation and female patients who were pregnant, breastfeeding, or capable of bearing children and not using adequate contraception were excluded.

Procedures

Subjects received open-label lamotrigine for 12 weeks, including a 5-week initiation/titration phase and a 7-week continuation phase. Lamotrigine was titrated in accordance with the manufacturer's prescribing information to a target dosage of 200 mg/d (range, 100–400 mg/d). The target dosage was adjusted as appropriate for patients receiving valproate, or carbamazepine, phenytoin, primidone, or phenobarbital, with commercially available titration packs with targeted maintenance dosages of 100 and 400 mg/d, respectively.

The rate of titration or dosage of lamotrigine could be lowered during the 5-week titration period, but the addition of new medications or increases in dosages of concomitant medications to treat mood symptoms were not permitted. Dosages of concomitant medications could be reduced to control side effects. Any patient who needed another intervention to control mood symptoms was withdrawn from the study.

Measures and Statistics

Investigators assessed the patients' clinical response at screening (baseline) and after 5 and 12 weeks of lamotrigine therapy, using the Clinical Global Impression–Bipolar Version (CGI-BP) Scale,[25] adapted for this study. Subjects were instructed in the use of an interactive voice response system to record self-reported clinical status, cognitive function, and patient satisfaction with lamotrigine. Patients used the Medical Outcomes Study–Cognitive (MOS-Cog) Scale,[26,27] validated in the assessment of patients with bipolar disorder,[28] to assess cognitive function at baseline and week 12. The MOS-Cog is a 6-item questionnaire that evaluates cognitive well-being with respect to memory, attention, reasoning, and judgment along a 6-point Likert-type scale; mean scores were transformed linearly to a scale of 0 to 100, with 100 indicating the most favorable possible self-assessment of cognitive function.

All patients who received at least 1 dose of study medication and provided at least 1 assessment of clinical response while receiving the medication (intention-to-treat [ITT] population) were included in the analyses. Changes from baseline in MOS-Cog score within a group (ie, total ITT population, patients receiving and not receiving various concomitant medications, patients <65 and ≥ 65 years old) were analyzed using paired t tests. Analysis of covariance, controlling for baseline score, age (except for age analysis), sex, region, and baseline CGI-BP score for overall severity, was used to determine whether change from baseline MOS-Cog score differed between groups (eg, patients receiving and not receiving various concomitant medications). Correlations were used to determine the magnitude and statistical significance of the association between changes in cognitive function and clinical response.

RESULTS

Patients

Of the 1175 patients who received at least 1 dose of lamotrigine, 1139 (96.9%) provided at least 1 assessment of clinical response while receiving lamotrigine. The mean age (± SD) was 42.2 ± 13.1 years, with 96.5% of patients older than 18 years and, in the ITT population, 4% aged 65 years or older. The patient population was 64% female and 90% non-Hispanic white. Mean baseline CGI-BP overall severity score for the ITT population was 3.4 ± 1.32, indicating mild to moderate psychopathology. At the moment of lamotrigine initiation, patients were receiving a mean of 2.38 ± 1.45 prescription psychotropic medications. Of the 1175 patients in the safety population, 260 (22%) were receiving concomitant valproate; 352 (30%), concomitant antipsychotics; and 778 (66%), concomitant antidepressants. The most common reasons for early discontinuation in the study were adverse events (15%), loss to follow-up (3%), and voluntary withdrawal (4%).

Cognitive Function Scores

For the overall sample, mean MOS-Cog score was 52.1 ± 22.66 at baseline and 61.1 ± 22.58 at week 12

(Table 1); mean MOS-Cog score improved by 8.4 ± 22.55 points ($P < 0.0001$).

Mean improvement in MOS-Cog score was statistically significant ($P < 0.0001$) versus that at baseline for patients not receiving concomitant valproate, antipsychotics, or antidepressants (Table 1). There were no significant differences observed in degrees of improvement based on concomitant administration of valproate (adjusted mean difference = −0.14; 95% confidence interval [CI], −3.30 to 3.01; $P = 0.928$) or antidepressants (adjusted mean difference = 0.60; 95% CI, −2.19 to 3.39; $P = 0.673$). However, patients receiving lamotrigine and not receiving concomitant antipsychotics exhibited a small but significantly greater degree of improvement than patients who were receiving concomitant antipsychotics, even after controlling for baseline MOS-Cog score, baseline CGI-BP severity score, age, sex, and region (adjusted mean difference = 4.05; 95% CI, 1.30–6.81; $P = 0.0039$).

Among patients aged 65 years or older (n = 47), mean improvement in the MOS-Cog score was 6.1 ± 19.96 and approached statistical significance ($P = 0.07$). Patients younger than 65 years had lower MOS-Cog scores at baseline than those aged 65 years or older (51.7 vs. 60.6, respectively), showed a statistically significant increase in MOS-Cog score (mean, 8.5 ± 22.66; $P < 0.0001$) from baseline, and demonstrated a greater, though nonsignificant, improvement at week 12 than those aged 65 years or older (8.5 vs. 6.1, respectively; adjusted mean difference, −1.58; 95% CI, −8.15 to 4.99; $P = 0.637$).

After initiation of lamotrigine therapy, statistically significant improvement of MOS-Cog scores was observed among patients with an index depressed episode (mean change from baseline, 8.8 ± 21.97; $P < 0.0001$) or an index manic episode (mean change from baseline, 7.5 ± 22.62; $P = 0.0007$).

Correlational Analyses

In the ITT population, improvement of the MOS-Cog score showed a statistically significant correlation with improvement from baseline in CGI-BP severity scores for mania (correlation coefficient, −0.151; $P < 0.0001$), depression (correlation coefficient, −0.339; $P < 0.0001$), and overall severity (correlation coefficient, −0.320; $P < 0.0001$).

DISCUSSION

In this post hoc analysis, open-label lamotrigine was associated with significantly improved self-rated cognitive scores in patients with bipolar I disorder, whether or not they were receiving concomitant valproate, antipsychotics, or antidepressants. The clinical significance of this improvement is not known. This improvement is consistent with the observations of Khan et al[22] in the open-label phase of a study of patients with bipolar I disorder treated with lamotrigine, although that improvement was not corroborated by subsequent analysis from the study's randomized phase, which showed no statistically significant differences in cognition scores between patients receiving lamotrigine and those receiving lithium or placebo.[29]

Patients who were not receiving concomitant antipsychotics showed a small but statistically significant improvement in self-rated cognitive function scores as compared with patients who were receiving antipsychotics. Patients with bipolar disorder who are prescribed long-term treatment with an antipsychotic may constitute a distinct population with respect to their self-rated cognitive response.

TABLE 1. MOS-Cog Scores in the Total Sample and in Subgroups

Regimen	Baseline Mean ± SD (n)	Week 12* Mean ± SD (n)	Change From Baseline Mean ± SD (n)
Total sample	52.1 ± 22.6 (1137)	61.1 ± 22.58 (912)	8.4 ± 22.55† (912)
Patients with and without various concomitant medications			
With concomitant valproate	54.7 ± 23.07 (249)	62.5 ± 22.97 (193)	7.3 ± 23.92† (193)
Without concomitant valproate	51.4 ± 22.50 (888)	60.8 ± 22.47 (719)	8.7 ± 22.17† (719)
With concomitant antipsychotics	52.4 ± 22.64 (347)	58.4 ± 23.08 (283)	5.7 ± 23.17†‡ (283)
Without concomitant antipsychotics	51.9 ± 22.68 (790)	62.4 ± 22.26 (629)	9.6 ± 22.18† (629)
With concomitant antidepressants	51.8 ± 22.69 (758)	60.7 ± 22.39 (612)	8.6 ± 22.43† (612)
Without concomitant antidepressants	52.7 ± 22.62 (379)	62.0 ± 22.96 (300)	8.1 ± 22.83† (300)
Patients' ages, yrs			
<65	51.7 ± 22.69 (1090)	61.0 ± 22.78 (875)	8.5 ± 22.66† (875)
≥65	60.6 ± 20.44 (47)	65.0 ± 16.75 (37)	6.1 ± 19.96 (37)
Patients with an index depressed or manic episode			
Depressed	51.1 ± 22.80 (550)	60.6 ± 21.81 (435)	8.8 ± 21.97† (435)
Manic	56.6 ± 21.83 (140)	64.1 ± 22.45 (113)	7.5 ± 22.62§ (113)

*Includes patients who prematurely withdrew.
†$P < 0.0001$ vs baseline.
‡$P < 0.05$ change from baseline versus without concomitant antipsychotics.
§$P = 0.0007$ vs baseline.

We cannot, however, determine whether this less positive effect on self-rated cognitive improvement is clinically significant. This observation may be a direct adverse effect of antipsychotics on cognition or related to an unknown factor such as an overall symptom severity in the group receiving antipsychotics.

Patients 65 years or older did not experience statistically significant improvement in self-rated cognitive function during 12 weeks of lamotrigine therapy, although there was a trend toward improvement. The small number of elderly patients who entered or completed the study would, in any event, make it difficult to detect small changes in MOS-Cog scores. Furthermore, baseline MOS-Cog scores were higher in elderly patients, as seen in a previous analysis.[22] Age-related difference in coping mechanisms or the perception of cognitive impairment as less detrimental to their lifestyle was suggested as an explanation.[22] Further research is needed to examine age-related differences in self-rated cognitive scores and in responses to pharmacotherapy.

Lamotrigine treatment was associated with statistically significant improvement from baseline in MOS-Cog scores among patients with either a depressive episode or a manic index episode. Change in self-rated cognitive function scores was significantly correlated with improvement of clinical symptoms, with the strength of the association greater in depressive and overall symptoms than in mania. The difference may be in part caused by the patient sample, which had limited manic symptoms. The results of the present analysis add support to the strong association between cognitive complaints and depressive symptoms in patients with bipolar I disorder. However, we cannot determine whether the difference in the degree of self-rated cognitive improvement among the index-depressed patients versus the index-manic patients was caused by a greater effect in these patients on cognitive functioning via a distinct domain as the difference could also be a reflection of improvement in depressive symptoms.

This post hoc analysis has several limitations such as the open-label design and a large sample size that may afford statistically significant differences, which may or may not be clinically relevant. Other limitations of the analysis caused by the study design were that patients were receiving a variety of concomitant medication; MOS-Cog scores were not obtained before the start of concomitant therapies; and information regarding patients' duration of illness, time since diagnosis, or comorbidities were not captured. A potential limitation of the MOS-Cog score as a measure of cognitive status is that it is based on patients' assessment of their cognitive function over the past 4 weeks, and it may be affected by a reduced ability to recognize or recall effects of cognitive impairment on day-to-day functioning. Some studies[30,31] suggest that the MOS-Cog score correlates with objective measures of cognitive function, but studies specifically in patients with bipolar disorder are needed to better characterize the relationship between self-rated cognitive function scores and neuropsychological functioning in this population.

In summary, open-label lamotrigine at dosages of 100 to 200 mg/d was associated with improved self-rated cognitive function scores versus those at baseline in patients with bipolar I disorder. This effect was apparent in patients receiving lamotrigine whether or not they were receiving concomitant valproate, antipsychotics, or antidepressants. Patients receiving lamotrigine who were not receiving concomitant antipsychotics showed a greater increase in self-rated function cognitive scores than those who were receiving concomitant antipsychotics. Additional studies are needed to explore the clinical relevance of these findings.

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APPENDIX

Below is supplemental material to the article by Dr Neil S. Kaye and colleagues titled "Effect of Open-Label Lamotrigine as Monotherapy and Adjunctive Therapy on the Self-Assessed Cognitive Function Scores of Patients With Bipolar I Disorder" that appears in the August 2007 issue of the Journal (*J Clin Psychopharmacol*. 2007;27:387–391).

Check 1 box on each line.

Appendix A. Medical Outcomes Study-Cognitive Scale (MOS-Cog)*

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
	1	2	3	4	5	6
During the past 4 weeks, how much of the time did you have difficulties in reasoning and problem solving?	☐	☐	☐	☐	☐	☐
During the past 4 weeks, how much of the time did you forget things that happened recently?	☐	☐	☐	☐	☐	☐
During the past 4 weeks, how much of the time did you have trouble keeping your attention focused?	☐	☐	☐	☐	☐	☐
During the past 4 weeks, how much of the time did you have difficulties doing activities that involved concentration and thinking?	☐	☐	☐	☐	☐	☐
During the past 4 weeks, how much of the time did you become confused and start several actions at the same time?	☐	☐	☐	☐	☐	☐
During the past 4 weeks, how much of the time did you react too slowly to things that were said or done?	☐	☐	☐	☐	☐	☐

Scoring: $[(1 + 2 + 3 + 4 + 5 + 6)/36] \times 100$.

*The MOS-Cog Scale is based on a subset of questions from the MOS core set of measures of functioning and well-being, developed at the RAND Corporation as part of the MOS.[26,27]