

Effects of Lamotrigine on Neurocognitive Measures in Bipolar I Patients

Laksmi Yatham, The University of British Columbia, Vancouver, B.C.; Arifulla Khan, Northwest Clinical Research Center, Bellevue, Washington; Lawrence D. Ginsberg, Red Oak Psychiatry Associates, Houston, Texas; Gregory M. Asnis, Montefiore Medical Center Anxiety and Depression Clinic, Bronx, New York; Fred K. Goodwin, Center on Neuroscience, Medical Progress, and Society and George Washington University Medical Center, Washington, DC; Kimberly H. Davis, GlaxoSmithKline, Research Triangle Park, North Carolina.

ABSTRACT

Background: This analysis describes the effects of bipolar I disorder on self-reported neurocognitive measures and remediation of these deficits with lamotrigine therapy.

Methods: Data were derived from two clinical trials designed to assess the efficacy of lamotrigine as maintenance therapy for recently manic or depressed patients. During the open stabilization phase, patients received lamotrigine as monotherapy or as adjunctive therapy while other psychotropic drugs were discontinued. The Medical Outcomes Study Cognitive Scale (MOS-Cog) and the AB-Neurological Assessment Scale (AB-NAS) were used to measure cognitive functioning at baseline and at end of open-label phase. To examine the relationship between depressive and manic symptomatology and changes in cognitive functioning, Pearson correlation coefficients were computed.

Results: Patients in either depressive or manic phases had significant cognitive impairment. In both studies, combined use of lamotrigine with other concomitant psychotropic medications significantly improved the mean scores from baseline to the end of the open-label phase for the MOS-Cog and the AB-NAS ($p < 0.0001$). Among patients who took lamotrigine as monotherapy, the mean MOS-Cog score also improved significantly versus baseline (+31.8, or 75%, for depressed patients $p < 0.0001$ and +19.2, or 33%, for manic patients $p = 0.0002$) and for the AB-NAS (-20.5, or -58%, for depressed patients $p < 0.0001$ and -6.6, or -29%, for manic patients; $p = 0.044$). Cognitive impairment was significantly correlated with depression symptom severity based on HAM-D scores ($p < 0.0001$) but not with manic symptoms.

Conclusions: Treatment with lamotrigine monotherapy and as combined therapy was associated with improved cognitive functioning and reduced neurocognitive side effects, regardless of index mood polarity.

The following information concerns a use that has not been approved by the US Food and Drug Administration.

INTRODUCTION

It is well established that cognitive function is impaired during mood episodes in patients with bipolar disorder. Both manic and depressive mood episodes are associated with decrements in attention, verbal or non-verbal learning, and memory. The cause of cognitive impairment in bipolar disorder is thought to be multifactorial. Neuroimaging studies linking cognitive abnormalities to enlargement of the lateral ventricles and to changes in hippocampal and temporal lobe volume suggest that a progressive neuropathological process is at least partly responsible. The finding that magnitude of cognitive impairment in bipolar disorder is directly related to frequency and/or severity of mood episodes is consistent with a causal role of progressive disease-associated neuropathology. Comorbid conditions, particularly alcohol dependence, may also contribute to cognitive impairment in bipolar disorder, but the presence of cognitive deficits in both patients with and without a history of alcohol dependence suggests that alcohol abuse is not wholly responsible. Neurological side effects of psychopharmacologic medications also contribute to cognitive impairment. Lithium, for example, impairs short-term memory, long-term memory, and psychomotor function in patients with bipolar disorder as well as in healthy subjects. Similarly, valproate and carbamazepine are associated with deficits in attention, memory, and information-processing. Pharmacotherapies for bipolar disorder should be chosen to minimize neurocognitive side effects and prevent further impairment of cognitive function, which may already be compromised by the disease. While the negligible effects of lamotrigine on cognitive function in healthy volunteers and patients with epilepsy are well defined, its neurocognitive effects in patients with bipolar disorder have not been reported.

OBJECTIVE

The primary objective of this analysis was to determine the effects of resolution of an acute depressive and an acute manic episode on cognitive functioning after treatment with lamotrigine monotherapy and combined use of lamotrigine with acute psychotropic medications based on the acute open-label stabilization phase from the two large clinical trials. It was hypothesized that acute episodes of mania and depression are associated with cognitive impairment and that successful acute treatment should remediate these cognitive impairments.

METHODS

• Two 18-month, double-blind, placebo-controlled trials were conducted in 26 countries to compare lamotrigine and lithium as maintenance treatment in bipolar I disorder. One-hundred fifty-nine institutions in 26 countries participated in the trials.

• Each study enrolled adult (aged > 18 years) outpatients who were either currently or recently depressed (GW605/2003) or who were currently or recently manic, hypomanic or had mixed mood states (GW606/2006) by DSM-IV criteria within 60 days of screening.

• Patients were evaluated for study enrollment during a 2-week screening phase. Those meeting enrollment criteria then completed an 8 to 16 week open-label phase during which all patients received lamotrigine (target dose 200mg/day, minimum dose 100mg/day) as monotherapy or as adjunctive therapy while other psychotropic drugs were discontinued.

• To assess cognitive functioning, the Medical Outcomes Study Cognitive Scale (MOS-Cog) and the AB-Neurological Assessment Scale (AB-NAS) were administered at enrollment and at the end of the open-label phase.

• The MOS-Cog is a 4-item questionnaire that measures cognitive well-being in the domains of memory, attention, judgement, and reasoning abilities. Patients responded to questions using a 6-point Likert-type response format, where total scores range from 0 (worse cognitive health) to 100 (best cognitive health).

• The AB-NAS is a 24-item questionnaire that measures adverse effects of medications on cognitive function in the domains of tiredness/fatigue, hyperexcitability, motor and mental slowing, memory impairment, attention disorders, impairment of motor coordination, and language disorders. Patients recorded their responses on a 4-point Likert-type scale (0=no problem; 3= a serious problem). Total score, obtained by summing scores for all questions, ranges from 0 (least impairment) to 72 (greatest impairment).

• Descriptive statistics were used to report cognitive-related adverse events experienced during the open-label phase for both studies and to characterize observed mean MOS-Cog and AB-NAS scores for the intent-to-treat population.

• A paired t-test was used to test mean changes in the MOS-Cog and the AB-NAS in all patients from baseline to the end of the open-label phase for each study and in patients who took only lamotrigine without any concomitant use of other adjunctive psychotropic medications.

• Pearson correlation analyses were used to test the association between cognition scores and symptom severity based on the HAM-D and the MRS at baseline and at the end of the open-label phase for all patients.

• A p-value of <0.05 was considered statistically significant.

RESULTS

• Of the 966 recently depressed patients who enrolled in the open-label phase (GW605/2003), 480 (50%) completed it. Of the 349 recently hypomanic/manic/mixed patients enrolled in the open-label phase (GW606/2006), 184 (54%) completed it. Demographic and clinical characteristics generally were comparable between the studies (Table 1).

• The incidence of somnolence during the open-label phase was 9% in index depressed patients and 10% in index manic patients. The incidence of fatigue reported as an adverse event during the open-label phase was 6% in index depressed patients and 5% in index manic patients.

• Psychotropic medications other than lamotrigine were used during the open-label phase by 81% of patients in GW205/2003 and 78% of patients in GW606/2006. Medications used by 10% or more index depressed patients during the open-label phase included antidepressants (49%), benzodiazepines (42%), lithium (20%), antipsychotics (24%), and valproate (13%). Medications used by 10% or more index manic patients during the open-label phase included lithium (18%), lorazepam (18%), clonazepam (15%), valproate (14%), and haloperidol (14%).

• Mean MOS-Cog Scores at baseline and at the end of the open-label phase reflect the magnitude of clinical severity measured by the HAM-D questionnaire for both studies (Figure 1). At baseline, very severely depressed patients (HAM-D score > 23) had the lowest mean MOS-Cog scores while mildly depressed patients (HAM-D score 8-13) had the highest mean MOS-Cog score. Likewise, patients with index mania who had minimal depression (HAM-D < 7) had the highest mean MOS-Cog scores compared with patients who were diagnosed with mild or moderate depression.

• The observed mean MOS-Cog score at baseline (n=316) in the intent-to-treat (ITT) population was 38.7 among index depressed patients and 69.2 (n=299) at end of open-label phase. The observed mean MOS-Cog score at baseline (n=117) in the intent-to-treat (ITT) population was 58.0 among index manic patients and 78.9 at end of open-label phase (n=112).

• At the end of the open-label phase, the MOS-Cog mean score improved significantly versus baseline in both studies (+30.2, or 79%, for index depressed patients and +21.2, or 36%, for index manic patients; $p < 0.0001$) (Figure 2).

• In patients who took lamotrigine as monotherapy without concomitant use of any other adjunctive psychotropic medication during the open-label phase, the mean observed MOS-Cog score at baseline was 41.7 among index depressed patients (n=71) and 58.0 among index manic patients (n=37). The mean MOS-Cog score improved significantly versus baseline in both studies (+31.8, or 76%, for index depressed patients $p < 0.0001$ and +19.2, or 33%, for index manic patients $p = 0.0002$).

• At the end of the open-label phase, Mean AB-NAS scores were significantly correlated ($p < 0.0001$) with depression severity symptoms as measured by the HAM-D, but there was minimal association of mean AB-NAS scores with manic symptom severity as measured by the MRS.

• Mean AB-NAS score at baseline (n=276) was 37.2 in index depressed patients and 22.9 in index manic patients (n=106). At the end of open-label phase, mean AB-NAS scores improved significantly versus baseline in both studies (-19.2, or -52%, for index depressed patients and -9.1, or 43%, for index manic patients; $p < 0.0001$) (Figure 3).

• Among lamotrigine monotherapy patients, mean AB-NAS scores at baseline was 35.3 in index depressed patients (n=66) and 22.6 in index manic patients (n=31). At the end of open-label phase, AB-NAS scores improved significantly versus baseline in both studies (-20.5, or 58%, for index depressed patients $p < 0.0001$ and -6.6, or -29%, for index manic patients; $p = 0.04$).

Figure 1. Mean MOS-Cog scores based on severity of clinical depression as measured by HAM-D for each study

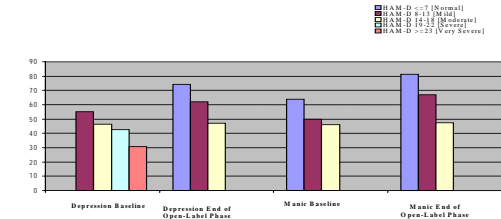


Figure 2. Comparison of mean MOS-Cog scores of all patients at baseline and at the end of the open-label phase in the index depressed and index manic studies

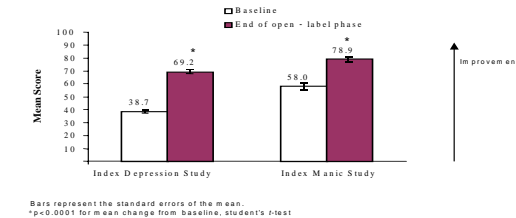
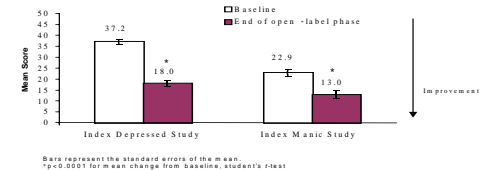


Figure 3. Comparison of mean AB-NAS scores for all patients at baseline and at the end of the open-label phase in the index depressed and index manic studies



CONCLUSIONS

- The first assessment of the effects of lamotrigine on standardized neurocognitive measures in bipolar patients suggests that lamotrigine monotherapy and conversion from other psychotropic treatments to lamotrigine is associated with significantly improved cognitive functioning.
- Improvement was greater in index depressed patients, whose mean MOS-Cog scores improved by nearly 80% from baseline (31-point change) and mean AB-NAS scores improved by more than 50% from baseline (19-point change).
- The results of this analysis show that cognitive impairment is more strongly related to severity of depressive symptoms than to severity of manic symptoms.

REFERENCES

- Morice R. Brit J Psychiatry. 1990; 157:50-54
 Bulbena A, Bernios GE. Psychopharmacology 1993; 26:6-12
 Gruzeller J, Seymour K, Wilson L, et al. Arch Gen Psychiatry 1988; 45:623-629
 Hauser P, Altshuler LL, Berrettini W, et al. J Neuropsychiatry Clin Neurosci 1989; 1:128-134
 Andreasen NC, Swazey V, Flaum M, et al. Am J Psychiatry 1990; 147:893-900
 Ananth J, Ghadrian AM, Engelsmann F. Can J Psychiatry 1987; 32:312-216
 Shaw ED, Stokes PE, Mann JJ et al. J Abnorm Psychol 1987; 96:64-69
 Goldberg JF, Burdick KE. J Clin Psychiatry 2001; 62(Suppl 14):27-33

Table 1. Demographics and Baseline Clinical Characteristics	Index Depressed (GW 605/2003)	Index Manic (GW 606/2006)
Enrolled in open-label phase, n	480	349
Completed open-label phase, n (%)	480 (50%)	184 (53%)
Reason for premature discontinuation, n (%)		
Adverse event	127 (13%)	42 (12%)
Consent withdrawn	128 (13%)	29 (8%)
Lost to follow-up	60 (6%)	30 (9%)
Did not meet randomization criteria	54 (6%)	25 (7%)
Protocol violation	20 (2%)	9 (3%)
Other	97 (10%)	29 (8%)
Mean (SD) age, years	42.2 (12.2)	40.7 (11.8)
Male, n (%)	372 (83%)	172 (50%)
Ever hospitalized for mood disturbance, n (%)	628 (66%)	230 (66%)
Ever attempted suicide, n (%)	353 (37%)	102 (29%)
Mean (SD) age of first depression, years	22.7 (11.6)	23.4 (12.1)
Mean (SD) age of first manic/mixed episode, years	26.7 (12.5)	26.0 (11.8)
Mean (SD) number of mood episodes in past year		
Depression	1.7 (0.7)	1.0 (0.8)
Mania	0.9 (0.7)	1.4 (0.8)
Hypomania	0.3 (0.7)	0.3 (0.6)
Mixed	0.1 (0.4)	0.2 (0.5)