Effect of Lamotrigine on Cognitive Complaints in Patients With Bipolar I Disorder

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

Method: Data were derived from 2 clinical trials designed to assess the efficacy of lamotrigine as maintenance therapy for recently manic (N = 349) or depressed (N = 966) patients (DSM-IV criteria). During the 8- to 16-week open stabilization phase, patients received lamotrigine as monotherapy or as adjunctive therapy (target dose = 200 mg/day, minimum dose = 100 mg/day) 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 the end of the open-label phase. To examine the relationship between depressive and manic symptomatology, initiation of lamotrigine, and cognitive functioning, correlational analyses and analyses of covariance were conducted.

Results: Bipolar patients in both trials had significant cognitive impairment; however, it was much greater in index episode depressed bipolar patients compared with index episode manic patients. In both studies, substitution of lamotrigine for other psychotropic medications significantly improved the mean scores from baseline to the end of the open-label phase on the MOS-Cog and the AB-NAS ($p < .0001$). Among patients who took lamotrigine as monotherapy, the mean MOS-Cog score also improved significantly versus baseline (+32.2, or 81%, for depressed patients, $p < .0001$; and +19.9, or 35%, for manic patients, $p < .0001$). Mean AB-NAS scores (–19.7, or –55%, for depressed patients, $p < .0001$; and –7.2, or –32%, for manic patients, $p = .0062$) showed similar improvement. Cognitive impairment was significantly correlated with depression symptom severity based on Hamilton Rating Scale for Depression scores ($p < .0001$). After controlling for change in mood, age, gender, baseline score, duration of illness, and duration of use of other psychotropics, a significant improvement in cognition was observed during the open-label phase when lamotrigine was used as monotherapy/adjunctive therapy.

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

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The concept of cognition or cognitive function is highly abstract and has been defined in multiple terms: memory, perception, ability to reason, psychomotor ability, attention span, concentration, comprehension, problem solving, judgment, learning ability, mental alertness, and orientation in time and space.[1,2] Severe or moderately severe cognitive problems can be observed easily by family, friends, and clinicians, while milder forms of cognitive impairment (e.g., forgetfulness, difficulty concentrating) may be perceived only by the patient.[3] It is well established that cognitive function is impaired during mood episodes in patients with bipolar disorder.[4–7] Both manic and depressive mood episodes are associated with decrements in attention, verbal and nonverbal learning, and memory. A growing body of evidence demonstrates that cognitive function is also impaired during euthymic intervals such that patients with bipolar disorder have deficient verbal and visuospatial memory and compromised executive and psychomotor functioning.[8–11]

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 neuropathologic process is at least partly responsible.[12–15] The finding that magnitude of cognitive impairment in bipolar disorder is directly related to frequency and/or severity of mood episodes[8,10] 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 patients both with and without a history of alcohol dependence[16] suggests that alcohol abuse is not wholly responsible. Neurologic 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.[9,17,18] Similarly, valproate and carbamazepine are associated with deficits in attention, memory, and information processing.[19]

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. Data available to date suggest that the anticonvulsant lamotrigine, marketed for the treatment of epilepsy and now established as effective in bipolar depression,[20–23] has a favorable neurocognitive profile. While the negligible effects of lamotrigine on cognitive function in healthy volunteers and patients with epilepsy are well defined,[19,24–29] its neurocognitive effects in patients with bipolar disorder have not been reported. Two randomized, double-blind, placebo-controlled studies[30,31] were conducted to assess the efficacy and tolerability of lamotrigine compared with the standard maintenance therapy, lithium, for prevention of relapse or recurrence of mood episodes in bipolar I patients. One study[30] enrolled patients who had currently or recently experienced a depressive episode (index depressed), while the second study[31] enrolled patients who had currently or recently experienced a hypomanic, manic, or mixed episode (index manic). The primary objective of the present 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 lamotrigine augmentation based on data from the acute open-label stabilization phase of the 2 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 this cognitive impairment.

METHOD

Patients

Two 18-month, placebo-controlled, double-blind clinical trials were prospectively designed to be combined for comparison of lamotrigine and lithium versus placebo as maintenance treatment in bipolar I disorder. Each study enrolled adult (≥ 18 years of age) outpatients who were either currently or recently depressed (GW605/2003) or who were currently or recently manic or hypomanic or had mixed mood states (GW606/2006) as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV).[32] These criteria had to be met within 60 days of screening. Separate reports of both clinical trials have been published elsewhere.[30,31] Patients with panic disorder, obsessive-compulsive disorder, social phobia, or bulimia nervosa in the year prior to study participation were excluded. Patients who were actively suicidal, had a score of ≥ 3 on item 3 of the 17-item Hamilton Rating Scale for Depression (HAM-D),[33] or had significant thyroid abnormality were also excluded.

Procedures

One hundred fifty-nine institutions in 26 countries participated in the 2 clinical trials, which were approved by an institutional review board or ethics committee at each site, and patients provided informed consent. The studies were conducted in 3 phases: a screening phase, an open-label phase, and a double-blind phase. Data for GW605/2003 were gathered from July 1997 to August 2001, and data for GW606/2006 were gathered from August 1997 to December 1999. 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 = 200 mg/day, minimum dose = 100 mg/day) as monotherapy or as adjunctive therapy while other psychotropic drugs were discontinued. The present study focused on the open-label treatment phase and the effects of lamotrigine on self-report neurocognitive measures, which were secondary endpoints.

Neurocognitive Measures

Subjective neurocognitive measures were obtained by administering the Medical Outcomes Study Cognitive Scale (MOS-Cog)[34] and the AB-Neurological Assessment Scale (AB-NAS)[35,36] at baseline (i.e., before initiation of open-label treatment with lamotrigine), at the end of the open-label phase, and at every protocol-scheduled visit throughout the double-blind phase. The MOS-Cog, previously shown to be reliable and valid in a sample of patients with bipolar disorder,[34] is a 6-item questionnaire that measures cognitive well-being in the domains of memory, attention, judgment, reasoning abilities, reaction time, and confusion. An abbreviated 4-item version, which excluded the last 2 items in the original 6-item version, was used in the current study. At the time the present studies were initiated, the necessary translations were available for only the first 4 items of the questionnaire, which were used previously in an infectious disease trial. Therefore,

this 4-item subset of the MOS-Cog questionnaire was used. It has not been previously validated, but the 4-item subset was part of the original validation study.[34] Patients responded to questions using a 6-point Likert-type response format, where total score ranges from 0 (worst cognitive health) to 100 (best cognitive health).

The AB-NAS, which was originally named the AB-Neurotoxicity scale, 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. The AB-NAS previously has been shown to be reliable and valid in patients with epilepsy.[35,36] Patients record their responses on a 4-point Likert scale (0 = no problem; 3 = a serious problem). The total score, obtained by summing the scores for all questions, ranges from 0 (least impairment) to 72 (greatest impairment). Although the clinical trials were international, the AB-NAS questionnaire was not translated from English and thus was administered only to patients who were fluent in English. The mean changes in MOS-Cog scores and AB-NAS scores from baseline to the end of the open-label phase constituted the main neurocognitive assessments of interest because these scores reflected cognitive function during the time that lamotrigine was first introduced and other psychotropics were discontinued.

Statistical Methods

Descriptive statistics were used to characterize observed mean MOS-Cog scores for the intent-to-treat population based on age, sex, duration of illness, and clinical severity as measured by the HAM-D. Mean scores also were characterized in a subset of patients with rapid cycling, defined as patients who reported 4 or more distinct mood episodes in the previous year. Pearson correlation analyses were used to test the association between cognition scores and symptom severity based on the HAM-D and the Mania Rating Scale (MRS) at baseline and at the end of the open-label phase for all patients. The association between mood and cognition at baseline was also examined in an analysis of covariance adjusted for age, gender, and psychotropic medication regimen at baseline (presence of benzodiazepines, antipsychotics, lithium, valproate, and other mood stabilizers). A paired t test was used to test mean changes in cognition in all patients from baseline to the end of the open-label phase for each study and in patients who took only lamotrigine with no concomitant use of other adjunctive psychotropic medications.

Analyses of covariance were also conducted to examine the association of lamotrigine monotherapy/adjunctive usage with change in cognition scores after controlling for the effects of baseline score, change in mood, duration of illness, age, gender, and duration of use of other psychotropics in the open-label phase. A similar analysis was performed for the subset of patients receiving lamotrigine as monotherapy.

Table 1. Demographics and Baseline Clinical Characteristics of Patients With Bipolar I Disorder

Characteristic	Index Episode Depressed (GW605/2003)	Index Episode Hypomanic/Manic/Mixed (GW606/2006)
Intent-to-treat population,[a] N	966	349
Completed open-label phase, N (%)	480 (50)	184 (53)
Reason for premature discontinuation, N (%)	484 (50)	164 (47)
Adverse event	128 (13)	42 (12)
Consent withdrawn	125 (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 (includes missing)	99 (10)	30 (9)
Safety population,[b] N	958	347
Age, mean (SD), y	42.2 (12.2)	40.7 (11.8)
Male, N (%)	370 (39)	172 (50)
Ever hospitalized for mood disturbance, N (%)	628 (66)	230 (66)
Ever attempted suicide, N (%)	353 (37)	102 (29)
Age at first depression, mean (SD), y	22.7 (11.6)	23.4 (12.1)
Age at first manic/mixed episode, mean (SD), y	26.7 (12.5)	26.0 (11.8)
Duration of bipolar illness, mean (SD), y[c]	20.4 (11.8)	18.6 (12.1)
No. of mood episodes in past year, mean (SD)		
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)

[a]All subjects enrolled in the open-label phase.
[b]All subjects receiving at least 1 dose of lamotrigine in the open-label phase.
[c]Statistically significant difference between studies (p = .0184).

RESULTS

Patients

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 (53%) completed it. Demographic and clinical characteristics, which have been reported elsewhere, generally were comparable between the studies (Table 1). Mean duration of illness was significantly greater in the index depressed trial compared with the index manic trial (p = .0184).

In both studies, the most common reason for discontinuation from the open-label phase was treatment-emergent adverse events, which could have been related to concomitant adjunctive medications or to lamotrigine.

Table 2. Mean MOS-Cog Scores by Age, Gender, Duration of Illness, and Presence of Rapid Cycling

Characteristic	Baseline		End of Open-Label Treatment	
	Index Episode Depressed (GW605/2003) (N = 672)[b]	Index Episode Manic[a] (GW606/2006) (N = 242)[c]	Index Episode Depressed (GW605/2003) (N = 299)[b]	Index Episode Manic[a] (GW606/2006) (N = 113)[c]
Age, y				
18–24	30.8	54.7	66.9	70.0
25–45	35.5	51.9	68.9	78.3
> 45	42.9	61.9	69.9	80.9
Gender				
Female	35.8	51.0	69.7	75.1
Male	40.2	58.7	68.6	82.8
Duration of illness, y				
< 5	33.9	59.8	68.6	73.6
5–10	35.6	55.6	71.6	71.5
11–20	37.5	54.7	68.7	79.5
> 20	38.6	53.9	69.0	82.1
With rapid cycling	33.3	50.1	67.4	77.0
Without rapid cycling	39.2	57.0	70.0	79.3
All patients[d]	37.5	54.9	69.2	78.6

[a]Patients with a hypomanic, manic, or mixed index episode.
[b]Intent-to-treat population with MOS-Cog data available at baseline.
[c]Intent-to-treat population with MOS-Cog data available at end of open-label phase.
[d]Statistically significant difference between studies at baseline ($p < .0001$) and at end of open-label phase ($p = .0002$).
Abbreviation: MOS-Cog = Medical Outcomes Study Cognitive Scale.

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 as a reported adverse event during the open-label phase was 6% in index depressed patients and 5% in index manic patients.

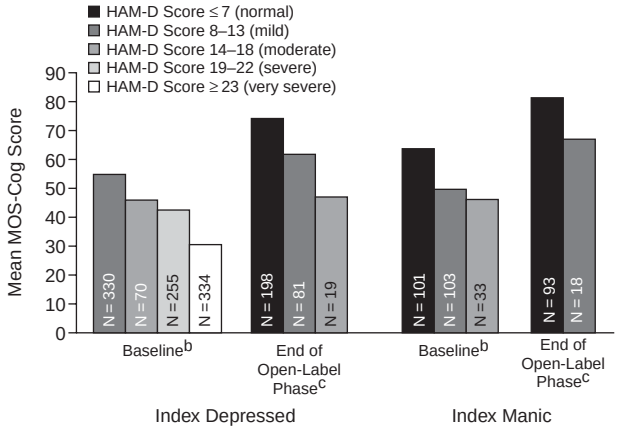
Psychotropic medications other than lamotrigine were used during the open-label phase by 81% of patients in GW605/2003 and 78% of patients in GW606/2006. Medications used by 10% or more index depressed patients during the open-label phase included antidepressants (49%), benzodiazepines (42%), mood stabilizers (37%), and antipsychotics (24%). Medications used by 10% or more index manic patients during the open-label phase included benzodiazepines (42%), mood stabilizers (48%), antipsychotics (44%), and anticholinergics (11%).

MOS Cognitive Scale

Table 2 displays mean MOS-Cog scores for the intent-to-treat population based on age, gender, duration of illness, and rapid cycling experienced in the year prior to study enrollment. Lower scores indicate greater cognitive impairment. At screening and at the end of the open-label phase, mean MOS-Cog scores were consistently higher in the older age groups (> 45 years) in both studies. Results showed minimal mean score differences based on gender; however, scores were somewhat higher in men. Mean scores also were similar at baseline and at the end of the open-label phase based on duration of illness. Mean scores for patients with rapid cycling were somewhat lower than scores for those without rapid cycling at baseline, but there were minimal differences at the end of the open-label phase for both studies. Index depressed patients scored significantly lower overall at baseline ($p < .0001$) and at the end of the open-label phase ($p = .0002$) as compared with index manic patients.

The 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 for both studies (Figure 1). At baseline, very severely depressed patients (HAM-D score of ≥ 23) had the lowest mean MOS-Cog scores, while mildly depressed patients (HAM-D score of 8–13) had the highest mean MOS-Cog scores. Likewise, patients with index mania who were not depressed (HAM-D score of ≤ 7) had the highest mean MOS-Cog scores compared with patients who were diagnosed with mild or moderate depression. Although sample size differences existed in both studies within each of the clinical severity categories, mean MOS-Cog scores reflected similar effects of depression on cognition regardless of index mood polarity. MOS-Cog scores at baseline and at the end of the open-label phase in each study were significantly inversely correlated ($p = .0001$) with scores on the HAM-D (Table 3). MOS-Cog scores at baseline and at the end of the open-label phase in each study were also significantly inversely correlated ($p < .05$) with MRS scores with 1 exception: cognition at baseline for index manic patients was not significantly correlated with the MRS (see Table 3). The analysis of covariance models showed that baseline depression score and age were the only significant predictors of MOS-Cog score at baseline for both index depressed patients ($p < .0001$ and $p = .0220$, respectively) and index manic patients ($p = .0001$ and $p = .0450$, respectively), while the effects of gender, baseline mania

Figure 1. MOS-Cog Scores[a] by Severity of Clinical Depression as Measured by the HAM-D for Each Study



[a]Mean values based on small sample sizes (N <10) were omitted.
[b]Intent-to-treat population with MOS-Cog data available at baseline.
[c]Intent-to-treat population with MOS-Cog data available at end of open-label phase.
Abbreviations: HAM-D = Hamilton Rating Scale for Depression, MOS-Cog = Medical Outcomes Study Cognitive Scale.

Table 3. Correlation Analysis of MOS-Cog and AB-NAS With HAM-D and MRS[a]

	HAM-D		MRS	
Scale	r	p	r	p
MOS-Cog				
Depressive index episode (GW605/2003)				
Baseline (N = 316)	–0.31	< .0001	–0.11	.046
End of open-label phase (N = 299)	–0.41	< .0001	–0.11	.048
Manic index episode (GW606/2006)[b]				
Baseline (N = 117)	–0.35	.0001	–0.11	.236
End of open-label phase (N = 112)	–0.47	< .0001	–0.32	.0006
AB-NAS				
Depressive index episode (GW605/2003)				
Baseline (N = 276)	0.33	< .0001	0.07	.272
End of open-label phase (N = 271)	0.43	< .0001	0.16	.010
Manic index episode (GW606/2006)[b]				
Baseline (N = 106)	0.43	< .0001	0.17	.083
End of open-label phase (N = 110)	0.39	< .0001	0.11	.261

[a]Intent-to-treat population. Ns differ in each pairwise correlation analysis due to missing data for AB-NAS/MOS-Cog and HAM-D/MRS.
[b]Patients with a hypomanic, manic, or mixed index episode.
Abbreviations: AB-NAS = AB-Neurological Assessment Scale, HAM-D = Hamilton Rating Scale for Depression, MOS-Cog = Medical Outcomes Study Cognitive Scale, MRS = Mania Rating Scale.

score, and psychotropic regimen were not statistically significant (Table 4).

Table 5 summarizes the mean unadjusted and adjusted change in MOS-COG and AB-NAS scores during the open-label phase in which lamotrigine was substituted for other psychotropic medications. At the end of the open-label phase, the mean MOS-Cog score (unadjusted) improved significantly versus baseline in both studies (+30.2, or 77%, for index depressed patients and +21.2, or 36%, for index manic patients; $p < .0001$). In patients who took lamotrigine as monotherapy without concomitant use of any other adjunctive psychotropic medication during the open-label phase, the results were consistent (unadjusted score), showing a significant improvement versus baseline in both studies (+32.2, or 81%, for index depressed patients, $p < .0001$; +19.9, or 35%, for index manic patients, $p < .0001$). A comparison between the adjusted and unadjusted mean changes in cognition across both studies demonstrated an improvement in cognition even after controlling for age, gender, baseline score, change in mood, duration of illness, and duration of use of other psychotropics.

AB-Neurological Assessment Scale

The trends that were seen with the MOS-Cog scores were virtually identical to those for the AB-NAS scores. Higher scores for the AB-NAS reflect more severe neurologic impact on functioning. AB-NAS scores in both studies were greater in the severely clinically depressed patients compared with mildly or minimally depressed patients at baseline and at the end of the open-label phase. AB-NAS scores were significantly correlated ($p < .0001$) with depression severity symptoms as measured by the HAM-D, but there was minimal association of manic symptom severity as measured by the MRS with AB-NAS scores (significant only for end of open-label phase for index depressed patients, $p = .010$) (Table 3).

At the end of the open-label phase, mean AB-NAS scores improved significantly versus baseline in both studies (–19.2, or –51%, for index depressed patients and –9.1, or –41%, for index manic patients; $p < .0001$) (Table 5). Among lamotrigine monotherapy patients, similar improvement was seen (–19.7, or –55%, for index depressed patients, $p < .0001$; –7.2, or –32%, for index manic patients, $p = .0062$). The adjusted AB-NAS scores were practically identical to the unadjusted scores, suggesting lamotrigine monotherapy/adjunctive therapy was associated with an improvement in cognition after controlling for improvement in mood.

DISCUSSION

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 are associated with improved cognitive functioning. Improve-

Table 4. Relationship Between Mood and Cognition at Baseline (p values)[a]

	MOS-Cog		AB-NAS	
Predictor	Index Episode Depressed (GW605/2003)	Index Episode Manic[b] (GW606/2006)	Index Episode Depressed (GW605/2003)	Index Episode Manic[b] (GW606/2006)
Gender	.2920	.0563	.2453	.0778
Age	.0220	.0450	.5103	.2256
HAM-D score at baseline	< .0001	.0001	< .0001	< .0001
MRS score at baseline	.1936	.4191	.7960	.1404
Medication regimen at baseline				
Benzodiazepines	.5040	.9987	.5663	.4856
Antipsychotics	.2791	.3402	.7488	.5786
Lithium	.8003	.9846	.7107	.7735
Valproates	.3845	.8015	.9879	.8838
Other mood stabilizers	.1098	.7772	.7196	.7544

[a]Age, gender, and medication were control variables in the analyses, and $p < .05$ was considered statistically significant.
[b]Patients with a hypomanic, manic, or mixed index episode.
Abbreviations: AB-NAS = AB-Neurological Assessment Scale, HAM-D = Hamilton Rating Scale for Depression, MOS-Cog = Medical Outcomes Study Cognitive Scale, MRS = Mania Rating Scale.

Table 5. Change in Cognition Between Baseline and End of Open-Label Phase in Patients Who Received Lamotrigine as Monotherapy or Adjunctive Therapy

	Unadjusted		Adjusted[a]	
Therapy	Mean Change	p Value	Mean Change	p Value
Lamotrigine monotherapy or adjunctive therapy				
Depressive index episode (GW605/2003)				
MOS-Cog (N = 289)	30.24	< .0001	30.14	< .0001
AB-NAS (N = 251)	–19.23	< .0001	–19.25	< .0001
Manic index episode (GW606/2006)[b]				
MOS-Cog (N = 110)	21.17	< .0001	21.26	< .0001
AB-NAS (N = 98)	–9.09	< .0001	–9.24	< .0001
Lamotrigine monotherapy				
Depressive index episode (GW605/2003)				
MOS-Cog (N = 123)	32.24	< .0001	32.29	< .0001
AB-NAS (N = 112)	–19.74	< .0001	–19.72	< .0001
Manic index episode (GW606/2006)[b]				
MOS-Cog (N = 47)	19.89	< .0001	19.74	< .0001
AB-NAS (N = 41)	–7.15	.0062	–7.21	< .0001

[a]Mean change adjusted for age, gender, baseline score, change in HAM-D and MRS scores, duration of bipolar illness, and duration (in days) of treatment with benzodiazepines, antipsychotics, lithium, valproates, and other mood stabilizers. Duration of treatment with concomitant medication was not included in monotherapy models.
[b]Patients with a hypomanic, manic, or mixed index episode.
Abbreviations: AB-NAS = AB-Neurological Assessment Scale, HAM-D = Hamilton Rating Scale for Depression, MOS-Cog = Medical Outcomes Study Cognitive Scale, MRS = Mania Rating Scale.

ment was greater in index depressed patients, whose mean MOS-Cog scores improved by nearly 80% from baseline (30-point change) and mean AB-NAS scores improved by more than 50% from baseline (19-point change). The magnitude of improvement in the AB-NAS scores was comparable to that previously defined as being clinically relevant among patients with epilepsy.[35–37]

The magnitude of cognitive impairment in bipolar disorder is directly related to the frequency and/or severity of mood episodes.[8,10] The results of this analysis show that cognitive impairment is more strongly related to severity of depressive symptoms than to severity of manic symptoms. Although patients with rapid cycling did show more cognitive impairment during an acute mood episode, restoration of cognition at the end of the open-label phase was very similar to that in patients without rapid cycling. Interestingly, while cognitive scores varied little based on duration of illness, patients older than 45 reported less cognitive impairment compared with younger patients. This pattern of results may be attributed to age-related differences in coping mechanisms, or impairment may be perceived as more detrimental to the lifestyle of younger patients. Cognitive impairment also was much greater in index depressed bipolar patients compared with index manic/hypomanic/mixed patients.

The correlation between self-reported cognitive function and HAM-D scores raises the question of whether self-report really reflects cognition or perception of cognition is distorted by depression. Piazzini et al.[38] showed that a self-report memory questionnaire showed no correlation with objective neuropsychological tests in epilepsy patients, but this discrepancy was not seen in

healthy controls. However, the self-report memory questionnaire was significantly correlated with the MRS, the HAM-D, the State-Trait Anxiety Inventory, and the Zung Self-Rating Depression Scale in epilepsy patients as well as in the control group. Given that lamotrigine was superior to placebo in delaying depressive episodes in the randomized phase in both studies, perhaps the improvement in MOS-Cog and AB-NAS scores does not reflect cognitive change but potentially reflects depression change or improvement of depression symptoms in both index depressed and index manic patients. However, in the analysis of covariance models, even after controlling for change in mood from baseline to the end of the open-label phase, an improvement in cognition was observed.

Besides appearing to be less cognitively impairing than other psychotropic medications, lamotrigine also may have direct cognitive-enhancing effects as suggested by anecdotal reports of "brightening" and improved mood and cognitive function among patients with refractory epilepsy treated with adjunctive lamotrigine.[39] The mechanism of lamotrigine-associated enhancement in cognitive function is unknown but possibly relates to a neuroprotective effect of the drug.[40,41] Whether lamotrigine could slow or arrest the neuropathologic changes and/or the long-term cognitive decline in bipolar disorder warrants additional study. Cognitive functioning is very important for the patient because even subtle cognitive dysfunction can impair an individual's working ability, social interactions, and creativity, and it often leads to medication noncompliance.[42]

The results of the current analysis should be interpreted within the context of the study. First, the degree to which improvement in cognitive function is attributable to the substitution of lamotrigine for other medications, as opposed to a direct enhancement of cognition by lamotrigine, is difficult to determine. Improvement in cognitive functioning could simply be due to the resolution of a patient's acute episode. Second, both of the neurocognitive measures involved patients' self-reports of cognitive function rather than direct assessments of objective cognitive performance, and the questionnaires have not been fully validated in bipolar patients. Last, upon entering the trial, the majority of patients were taking at least 1 concomitant psychotropic or nonpsychotropic medication, which could potentially have been cognitively impairing and thus reflect greater cognitive impairment scores at baseline. However, the analyses of covariance demonstrated that psychotropic regimen at baseline and duration of use of another psychotropic during the open-label phase did not impact cognition scores in most models. Future research might improve on the current analysis by using double-blind placebo-controlled methodology as well as prospective objective measurements of cognitive performance. Although an analysis of the mean change in MOS-Cog score and AB-NAS score based on the randomization phase was planned, the ability of the studies to detect treatment differences in cognitive functioning was limited due to the small sample size, which was insufficient to provide a meaningful comparison at the end of 18 months. The small sample size was directly related to loss of patients by withdrawal of consent and loss to follow-up over 18 months as well as optional patient discontinuation due to the occurrence of a new mood episode. These shortcomings notwithstanding, the consistency with the data on lamotrigine use in healthy volunteers and patients with epilepsy lends credence to these preliminary results.[24,37,43–44]

In conclusion, clinically significant improvements in cognitive function and reductions in neurocognitive side effects were observed with open-label treatment with lamotrigine as monotherapy and as adjunctive therapy in patients with bipolar I disorder. Patients who were recently depressed experienced the greatest magnitude of improvement.

Drug names: carbamazepine (Carbatrol, Tegretol, and others), lamotrigine (Lamictal), lithium (Lithobid, Eskalith, and others).

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