Efficacy and Safety of Lamotrigine as Add-On Treatment to Lithium in Bipolar Depression: A Multicenter, Double-Blind, Placebo-Controlled Trial

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Objective: Lamotrigine is one of the pharmacologic options for the treatment of bipolar depression but has only been studied as monotherapy. This study compared the acute effects of lamotrigine and placebo as add-on therapy to ongoing treatment with lithium in patients with bipolar depression.

Method: Outpatients (N = 124) aged 18 years and older with a DSM-IV bipolar I or II disorder and a major depressive episode (Montgomery-Asberg Depression Rating Scale [MADRS] score ≥ 18 and Clinical Global Impressions-Bipolar Version [CGI-BP] severity of depression score ≥ 4) while receiving lithium treatment (0.6–1.2 mmol/L) were randomly assigned to 8 weeks of double-blind treatment with lamotrigine (titrated to 200 mg/d) or placebo. The primary outcome measure was mean change from baseline in total score on the MADRS at week 8. Secondary outcome measures were response (defined as a reduction of ≥ 50% on the MADRS and/or change of depression score on the CGI-BP of "much improved" or "very much improved" compared to baseline) and switch to mania or hypomania (defined as a CGI-BP severity of mania score of at least mildly ill at any visit). Patients were included in the study between August 2002 (Spain started in October 2003) and May 2005.

Results: Endpoint mean change from baseline MADRS total score was –15.38 (SE = 1.32) points for lamotrigine and –11.03 (SE = 1.36) points for placebo (t = –2.29, df = 104, p = .024). Significantly more patients responded to lamotrigine than to placebo on the MADRS (51.6% vs. 31.7%, p = .030), but not on the CGI-BP change of depression (64.1% vs. 49.2%, p = .105). Switch to mania or hypomania occurred in 5 patients (7.8%) receiving lamotrigine and 2 patients (3.3%) receiving placebo (p = .441).

Conclusion: Lamotrigine was found effective and safe as add-on treatment to lithium in the acute treatment of bipolar depression.

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Patients with bipolar disorder spend more time depressed than manic or hypomanic,[1–4] while most mood stabilizers (lithium, valproate, carbamazepine) are more effective against manic episodes than depressive episodes.[5–7] The same appears true for atypical antipsychotics, although olanzapine (alone as well as in combination with fluoxetine[8]) and quetiapine[9] have demonstrated efficacy in the acute treatment of bipolar depression.

As a consequence, many bipolar patients also receive antidepressants, mostly in combination with other therapies. The finding that the effect size for the combination

of olanzapine with fluoxetine was superior to the effect size of olanzapine monotherapy underscores the importance of combination therapy studies.[10] While some studies found that antidepressants, either as monotherapy or combination therapy with mood stabilizers, are effective in the treatment of acute bipolar depression,[11] other studies found no effect of the addition of antidepressants to mood stabilizers.[12,13] In addition, their use may be associated with the risk of switch to mania or hypomania.[11,14]

The anticonvulsant lamotrigine provides an additional treatment option. After a few case reports and some open-label studies,[15–17] the first double-blind randomized controlled trial[18] on the efficacy of lamotrigine monotherapy in the acute treatment of bipolar depression found it more effective than placebo at doses of 50 and 200 mg/day on several secondary outcome measures, including the Montgomery-Asberg Depression Rating Scale (MADRS), but not on the primary outcome measure, i.e., the Hamilton Rating Scale for Depression (HAM-D). Subsequently, its efficacy in the acute treatment of bipolar depression was studied in 4 other randomized controlled trials. Although those studies were all negative on the primary outcome criterion,[19] a meta-analysis of the 5 studies showed a small but significant positive result.[20,21] In another study, lamotrigine was slightly less effective but better tolerated than a combination of olanzapine and fluoxetine.[22] Collaborative results were also obtained from a crossover study that compared lamotrigine and gabapentin to placebo.[23] In 2 long-term studies of bipolar I patients with a current (or recent) manic or depressive episode,[24,25] lamotrigine (titrated up to 200–400 mg/day) was added to ongoing treatment with other psychotropic drugs over 8 to 16 weeks. Concomitant drugs were gradually withdrawn, after which stabilized patients were randomly assigned to continuation of lamotrigine or to lithium or placebo (each as monotherapy) for up to 18 months. In both studies, lamotrigine and lithium were statistically more effective than placebo on the primary outcome measure (time from randomization to intervention for any mood episode), but lithium was predominantly effective against manic episodes and lamotrigine predominantly against depressive episodes, suggesting that lithium and lamotrigine have differential and potentially complementary effects.

In this article, we report the results of the first placebo-controlled study addressing the efficacy and safety of lamotrigine as add-on to lithium in the acute treatment of patients with bipolar depression.

METHOD

Study Design

This study is the first phase of an investigator-initiated (W.A.N.) randomized, double-blind, placebo-controlled trial, with 23 recruiting centers (of 25 selected) in the Netherlands and 3 recruiting centers (of 5 selected) in Spain.

Recruitment took place between August 2002 and May 2005 (Spain started in October 2003). The study was approved by the ethical review board of the University Medical Center Utrecht, the Netherlands, and by local institutional review boards in both countries. All patients gave written informed consent prior to initiation of any study procedure.

Patients

Outpatients (men or women) aged 18 years or older could be included if they met criteria for DSM-IV bipolar I or II disorder, current major depressive episode confirmed by the Mini-International Neuropsychiatric Interview Plus (MINI-Plus),[26] with a score of ≥ 18 points on the MADRS[27] and a score of ≥ 4 (moderately ill) on the Clinical Global Impressions-Bipolar Version (CGI-BP) severity of depression rating.[28] All patients had to be receiving treatment with lithium with a stable dose (plasma level, 0.6–1.2 mmol/L) during at least 2 weeks prior to the study.

Exclusion criteria were the following: the presence of psychotic features, a severe rapid cycling course with ≥ 10 episodes over the last 12 months (rapid cycling with 4–9 episodes in the previous 12 months was allowed), severe suicidality (score of ≥ 5 on item 10 of the MADRS), a history of alcohol or substance abuse within 1 month or dependence within 12 months of enrollment, a severe personality disorder suggesting noncompliance, or a severe neurologic or other somatic illness and the use of somatic medication that could affect mood. Women of child-bearing potential were only eligible for the study if they had a negative pregnancy test at screening and agreed to utilize an effective contraceptive method. Except for lithium, patients were not allowed to have used an antipsychotic or an antidepressant within 2 weeks (fluoxetine, 4 weeks) of randomization. Benzodiazepines were allowed at a maximum of 2-mg lorazepam equivalents per day throughout the study, i.e., for standing as well as rescue medication, for anxiety, agitation, or sleep problems.

Treatments

After inclusion in the study, patients were randomly assigned 1:1 to either lamotrigine or placebo in blocks of 2 as adjunctive treatment to ongoing treatment with lithium according to a randomization list. Stratification was done by site. The code of each patient was kept in a sealed envelope at the pharmacy of each participating center and could be opened by the pharmacist only in case of medical emergency. The study blind was preserved until after the last patient evaluation.

Study medication was administered once daily in the morning. Lamotrigine was started at 25 mg/day in weeks 1 and 2 and was increased to 50 mg/day in weeks 3 and 4,

to 100 mg/day in weeks 5 and 6, and, finally, to 200 mg/day in weeks 7 and 8. Placebo was administered by utilizing tablets identical in appearance and number. The lithium dosage remained stable during the study with monitoring of plasma levels (to be kept at 0.6–1.0 mmol/L) at baseline and week 8.

To establish medication compliance, a pill count was done at every visit. Patients returning more than 30% of their prescribed medication or reporting an interruption of medication for more than 3 days were withdrawn from the study. Patients who missed their study medication for 1, 2, or (maximum) 3 days restarted at the same dose.

Outcome Measures

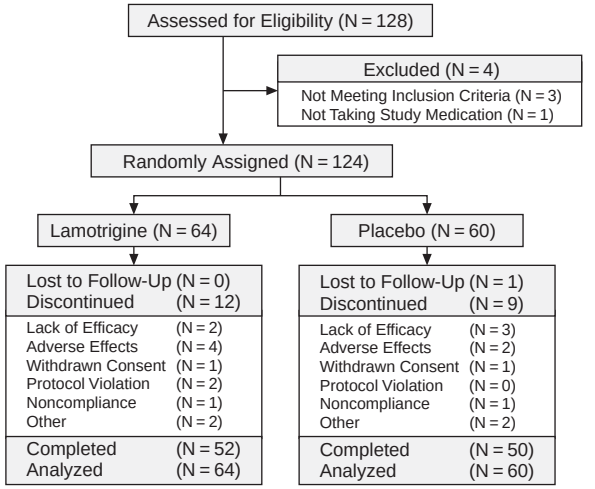
At baseline, diagnosis was confirmed with the MINI-Plus sections depressive episode, manic episode, hypomanic episode, alcohol abuse and dependence, and substance abuse and dependence. In addition, clinicians completed the Clinical Questionnaire for Bipolar Illness (CQBP-C), with items on illness and treatment history, as used by the former Stanley Foundation Bipolar Network.[29] Severity of symptoms was assessed at baseline and at weeks 2, 4, 6, and 8 by using the MADRS and the CGI-BP severity of depression and severity of mania. Adverse events were assessed at each visit by inquiring about any unpleasant feeling since the last visit and, if present, rated mild, moderate, or severe.

The protocol as well as the case record form were written in English but included validated Dutch and Spanish translations of the MADRS and the CGI-BP. In the Netherlands, there were 4 research meetings, including MADRS training sessions; 27 raters scored at least 4 patients with an intraclass coefficient = 0.95. After receiving an initial MADRS training in Spain, all Spanish researchers participated in a research meeting in the Netherlands with additional MADRS training.

The primary outcome measure was the mean change from baseline in total MADRS score at week 8. Secondary outcome measures were response (defined as a reduction of ≥ 50% on the MADRS and/or CGI-BP change of depression score of "much improved" or "very much improved" compared to baseline) and switch into mania or hypomania (defined as a CGI-BP severity of mania score of at least mildly ill at any visit). Post hoc, we also analyzed on which items of the MADRS there were significant differences between lamotrigine and placebo at week 8.

Switch to mania or hypomania is an undesirable outcome in the treatment of bipolar depression but can occur following recovery from depression. However, it often remains unclear in publications whether patients who switched were also counted as responders. Therefore, in a post hoc analysis, we assessed whether patients reached the criteria for both response (MADRS and/or CGI-BP change of depression) and no switch to mania or hypomania (CGI-BP), which is the ultimate goal in the treatment of bipolar depression.

Figure 1. Flow Chart of Patients Randomly Assigned to Lamotrigine or Placebo as Add-On Treatment to Lithium



The study was initially aimed at comparing 2 groups of 110 patients in order to detect a mean difference of 4 points in MADRS scores between the 2 groups, with 80% power and α of .05 (2-sided). The standard deviation (SD) of the MADRS score was initially set at 11 points. Because of difficulties in recruiting the planned number of patients, the sample size was recalculated after inclusion of a total of 43 patients. The MADRS scores based on these actually observed patients, who were evaluated blindly to outcome, resulted in an SD of 8 points and a corresponding recalculated sample size of 60 patients per group.

Analysis

Mixed-model analysis of variance (ANOVA) for repeated measures was prospectively chosen as method of analysis for MADRS scores. The independent variables in this analysis were time and treatment and their interaction. Time as categorical variable allowed estimating and testing mean differences in MADRS score between the 2 treatments at any visit, including the primary efficacy measure: score change from baseline at week 8. For this purpose the relevant contrasts were specified in the model for which the ANOVA produced the estimates, SEs, confidence intervals (CIs), and appropriate t tests per visit. In order to make inference about an overall treatment effect over all visits, time was considered a numeric trend variable in the model. This allowed estimating and testing a downward trend in time of the mean MADRS score in either treatment group and the difference in time trend between the 2 treatments as a single efficacy measure, for which the mixed-model ANOVA produced the estimate,

Table 1. Baseline Patient and Illness Characteristics in Patients Randomly Assigned to Lamotrigine or Placebo as Add-On Treatment to Lithium

	Lamotrigine (N = 64)		Placebo (N = 60)		Total (N = 124)					
Characteristic	N	%	N	%	N	%	Statistic	Value	df	p
Female gender	37	57.8	30	50	67	54.0	Fisher	…	…	.471
Age, y	45.2[a]	12.1[b]	47.6[a]	11.6[b]	46.4[a]	11.9[b]	t Test	1.13	122	.261
Illness characteristic										
Bipolar I disorder	43	67.2	41	68.3	84	67.7	Fisher	…	…	> .999
Rapid cycling course, last 12 mo	12	18.8	4	6.7	16	12.9	Fisher	…	…	.061
MADRS score	28.25[a]	5.97[b]	28.82[a]	6.24[b]	28.52[a]	6.08[b]	t Test	0.52	122	.606
CGI-BP severity of depression score	4.56[a]	0.64[b]	4.53[a]	0.57[b]	4.55[a]	0.60[b]	χ^2 Trend	0.07	1	.882
CGI-BP severity of mania score	1.03[a]	0.18[b]	1.03[a]	0.18[b]	1.03[a]	0.18[b]	Fisher	…	…	> .999
Previous treatment for index depressive episode										
Lithium										
Baseline plasma level, mmol/L	0.82[a]	0.16[b]	0.84[a]	0.16[b]	0.83[a]	0.16[b]	t Test	0.48	122	.634
Duration of treatment before randomization										
2–4 wk	1	1.9	4	8.0	…	…	Fisher	…	…	.347
> 1–3 mo	6	11.3	4	8.0	…	…	Fisher	…	…	.347
> 3 mo	46	86.8	42	84.0	…	…	Fisher	…	…	.347
Unknown/missing	11		10							
TCA	6	9.4	4	6.7	10	8.1	Fisher	…	…	.745
SSRI/SNRI	15	23.4	16	26.7	31	25.0	Fisher	…	…	.836
MAOI	1	1.6	3	5.0	4	3.2	Fisher	…	…	.353
Antipsychotic, typical	4	6.3	3	5.0	7	5.6	Fisher	…	…	> .999
Antipsychotic, atypical	15	23.4	11	18.3	26	21.0	Fisher	…	…	.317
Valproic acid	5	7.8	2	3.3	7	5.6	Fisher	…	…	.247
Carbamazepine	1	1.6	3	5.0	4	3.2	Fisher	…	…	.285
Benzodiazepine	44	68.8	35	58.3	79	63.7	Fisher	…	…	.154
Other	3	4.7	4	6.7	7	5.6	Fisher	…	…	.464

[a]Mean.
[b]SD.
Abbreviations: CGI-BP = Clinical Global Impressions-Bipolar Version, MADRS = Montgomery-Asberg Depression Rating Scale, MAOI = monoamine oxidase inhibitor, SSRI = selective serotonin reuptake inhibitor, SNRI = serotonin-norepinephrine reuptake inhibitor, TCA = tricyclic antidepressant.

SE, CI, and appropriate t test. In accordance with the intent-to-treat principle, all randomly assigned subjects contributed to these analyses, missing values of MADRS being properly adjusted for by the restricted maximum likelihood estimation procedure used in the mixed-model ANOVAs. Clinical Global Impression-Bipolar Version severity scores were similarly analyzed by using mixed-model ANOVA, with time as categorical variable. Dichotomous outcome scores (response, switch, or presence of adverse effects) were made complete by using the last-observation-carried-forward method and then were analyzed by comparing percentages between the 2 treatment groups using Fisher exact test. Differences in the distribution of categorical nominal variables between the 2 treatment groups were tested using Fisher exact test; for categorical ordinal variables the exact χ^2 trend test was used. For each test, a 2-sided p value below .05 was considered to denote statistical significance.

RESULTS

Patients and Illness Characteristics

In total, 128 patients were recruited (Figure 1): most patients (N = 82) from the 23 centers in the Netherlands, 34 patients via advertisements in Dutch newspapers, and 12 patients from the 3 centers in Spain. The range of included patients per center was between 1 and 25.

Four patients were not included in the analysis: at baseline, 1 patient appeared to use an antipsychotic; 1 patient had used an antidepressant in the 2 weeks before randomization; 1 patient had hypothyroidism; and 1 patient never took any medication. Thus, 124 patients were randomly assigned and included in the analysis: 64 patients to lithium plus lamotrigine and 60 patients to lithium plus placebo. There were no statistically significant differences between the 2 groups in patient characteristics and illness severity at baseline (Table 1). In both groups, more than 80% of the patients had been receiving lithium maintenance treatment for at least 3 months.

At baseline, lithium plasma levels were within the predefined range for 119 patients (0.6–1.2 mmol/L), while 5 patients had marginally lower plasma levels (all above 0.53 mmol/L). As these levels were only marginally lower than the required level of 0.6 mmol/L, a decision to include these patients in the analysis was made prior to breaking of the treatment blind. There was no significant difference between lithium plasma levels in the placebo group versus the lamotrigine group at baseline (t = 0.48, df = 122, p = .63; 0.84 [SD = 0.16] mmol/L and 0.82 [SD = 0.16] mmol/L, respectively) nor at 8 weeks

Table 2. Efficacy Results (mixed-model estimates): Severity Scales

	Lamotrigine (N = 64)		Placebo (N = 60)		Difference				
Measure	Mean	SE	Mean	SE	Mean	SE	t Test	df	p
MADRS score change from baseline (primary outcome measure)									
Wk 2	–5.30	0.87	–3.74	0.91	–1.56	1.26	–1.23	121	.220
Wk 4	–9.22	1.25	–6.24	1.29	–2.98	1.80	–1.66	110	.101
Wk 6	–12.84	1.35	–9.31	1.39	–3.53	1.90	–1.82	104	.071
Wk 8	–15.38	1.32	–11.03	1.36	–4.35	1.90	–2.29	104	.024
MADRS score at each visit									
Baseline	28.25	0.76	28.82	0.79	–0.57	1.10	–0.52	122	.606
Wk 2	22.95	1.02	25.08	1.06	–2.12	1.47	–1.44	121	.153
Wk 4	19.03	1.28	22.58	1.32	–3.55	1.84	–1.93	113	.056
Wk 6	15.41	1.30	19.50	1.34	–4.09	1.87	–2.19	106	.031
Wk 8	12.87	1.23	17.79	1.27	–4.92	1.77	–2.78	104	.006
CGI-BP severity of depression score at each visit									
Baseline	4.56	0.08	4.53	0.08	0.03	0.11	0.27	122	.789
Wk 2	4.14	0.14	4.15	0.14	–0.01	0.20	–0.03	121	.976
Wk 4	3.69	0.17	3.86	0.18	–0.17	0.24	–0.70	111	.486
Wk 6	3.07	0.18	3.48	0.19	–0.40	0.27	–1.52	104	.131
Wk 8	2.63	0.18	3.10	0.19	–0.47	0.26	–1.79	103	.077
CGI-BP change of depression score from baseline									
Wk 2	3.49	0.13	3.44	0.14	0.05	0.19	0.27	121	.788
Wk 4	3.37	0.16	3.46	0.17	–0.09	0.24	–0.37	101	.710
Wk 6	2.79	0.17	3.21	0.18	–0.42	0.25	–1.68	90	.097
Wk 8	2.52	0.19	2.96	0.19	–0.44	0.27	–1.65	117	.101
CGI-BP severity of mania score at each visit									
Baseline	1.03	0.02	1.03	0.02	0.00	0.03	–0.07	122	.948
Wk 2	1.11	0.04	1.07	0.04	0.04	0.06	0.68	121	.496
Wk 4	1.13	0.05	1.07	0.05	0.06	0.07	0.92	79	.360
Wk 6	1.07	0.03	1.07	0.03	0.00	0.05	0.08	54	.940
Wk 8	1.15	0.06	1.13	0.06	0.02	0.08	0.31	78	.757

Abbreviations: CGI-BP = Clinical Global Impressions-Bipolar Version, MADRS = Montgomery-Asberg Depression Rating Scale.

(t = 1.36, df = 100, p = .18; 0.80 [SD = 0.14] mmol/L and 0.76 [SD = 0.16] mmol/L, respectively).

In the lamotrigine group, 52 patients (81%) completed the 8-week study period versus 50 patients (83%) in the placebo group. Of the 12 patients who discontinued the trial in the lamotrigine group, 2 discontinued because of lack of efficacy and 4 because of adverse effects. In the placebo group, 10 patients discontinued the trial: 3 because of lack of efficacy and 2 because of adverse effects. Other reasons in both groups for discontinuing were withdrawn consent, protocol violation, noncompliance, and lost to follow-up.

Efficacy

Results are presented in Tables 2 and 3. On the primary outcome measure, change in the MADRS score from baseline to week 8, lamotrigine was significantly more effective than placebo (decrease of 15.38 vs. 11.03, respectively, p = .024) (Table 2). The lamotrigine group also had significantly lower MADRS scores at weeks 6 and 8 compared to the placebo group (Figure 2). Starting from an overall average baseline level of 28.4 points, the MADRS score decreased on average by 3.77 points per 2 weeks (95% CI = 3.15 to 4.38; p < .0005) during the first 8 weeks of treatment in the lamotrigine group. In the placebo group, the decrement was on average 2.59 points per 2 weeks (95% CI = 1.96 to 3.22; p < .0005). Hence, the mean MADRS score in the lamotrigine group became increasingly lower than the mean score in the placebo group by, on average, 1.17 points per 2 weeks (95% CI = 0.33 to 2.02; p = .007) during the first 8 weeks of treatment. Response, defined as a reduction of the MADRS score of ≥ 50%, was statistically greater (p = .03) in the lamotrigine group (51.6%) than in the placebo group (31.7%) (Table 3). Response according to CGI-BP change of depression scores ≤ 2 and response according to either criterion (MADRS and/or CGI-BP change of depression) showed no significant differences.

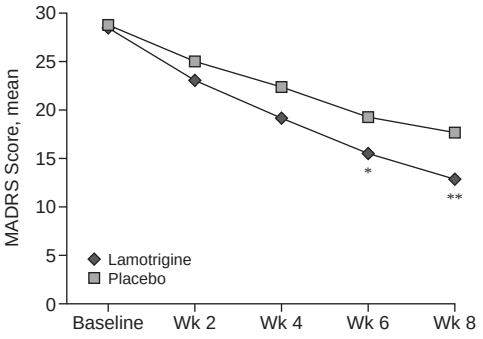
Because 12 patients (18.8%) receiving lamotrigine versus 4 patients (6.7%) in the placebo group had been rapid cyclers in the past year (difference approaching statistical significance [p = .06, Fisher exact test]), this subgroup was the subject of a post hoc analysis, revealing 8 (66.7%) lamotrigine and 1 (25%) placebo responders by MADRS and/or CGI-BP change of depression (p = .26, Fisher exact test). Four patients (25%) of the 16 rapid cycling patients (all 4 receiving lamotrigine) had a manic or hypomanic episode versus 3 patients (2.8%) of 108 non–rapid cycling patients (1 patient receiving lamotrigine, 2 patients receiving placebo). Over both treatment conditions, the switch rate to mania or hypomania was significantly higher in the rapid cycling versus the non–rapid cycling patients (p = .005, Fisher exact test).

Table 3. Efficacy Results: Response and Switch to Mania or Hypomania[a]

Outcome	Lamotrigine (N = 64) N	%	Placebo (N = 60) N	%	p[b]
Response					
Reduction MADRS ≥ 50%	33	51.6	19	31.7	.030
CGI-BP change of depression ≤ 2	41	64.1	29	49.2[c]	.105
Either or both	42	65.6	29	49.2[c]	.065
Switch to mania or hypomania[d]	5	7.8	2	3.3	.441
Response and no switch to mania or hypomania[e]	39	60.9	28	46.7	.149

[a]Adjusted for gender, bipolar disorder I/II, age, lithium, and rapid cycling.
[b]Fisher exact test.
[c]One participant missing.
[d]CGI-BP severity of mania score ≥ 3.
[e]Reduction MADRS score ≥ 50% and/or CGI-BP change of depression score ≤ 2 and CGI-BP severity of mania score < 3.
Abbreviations: CGI-BP = Clinical Global Impressions-Bipolar Version, MADRS = Montgomery-Asberg Depression Rating Scale.

Figure 2. Severity of Depression According to the Mean MADRS Score at Each Visit for Patients Receiving Placebo or Lamotrigine



*p = .031.
**p = .006.
Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale.

On the different MADRS items, there was a significant difference after 8 weeks between lamotrigine and placebo on apparent sadness, reported sadness, reduced appetite, lassitude, inability to feel, and suicidal thoughts. The sample size was too small to detect the following treatment-by-subgroup interactions: bipolar I versus II, rapid cycling versus non–rapid cycling, and severe versus less severe depression at baseline. A site-by-treatment analysis was not done as it was not foreseen in the protocol.

Safety

Five patients had a serious adverse event (SAE). One patient in the placebo group experienced a severe rash. As this was an unexpected finding, we checked the randomization code for possible mistakes and asked the laboratory to check the pills directly; both checks revealed that the medication was indeed placebo. So we decided that this was a chance finding. Four SAEs occurred in the lamotrigine group. One patient developed a manic psychotic episode requiring hospitalization. The episode resolved completely after stopping of the study medication and with additional treatment. The 3 other SAEs with lamotrigine involved 1 patient with severe hypertension that was considered to be unrelated to study drug, 1 patient with a nonsevere lithium intoxication (lithium level, 1.36 mmol/L, unexplained and probably not the result of an autointoxication), and 1 patient who had to be hospitalized due to deterioration of depressive symptoms. Study medication was continued in the patients with the lithium intoxication and the hypertension and was stopped in the other patients.

Other adverse events occurring in more than 5% in either group are presented in Table 4. Most of the adverse events were mild or moderate. There were no statistically significant differences between the 2 groups in occurrence of adverse events. In particular, there was no difference in the incidence of skin rash (4.7% for lamotrigine vs. 6.7% for placebo, p = .71).

Table 4: Adverse Events Occurring in ≥ 5% of Patients in Any Group

Adverse Event	Lamotrigine (N = 64) N	%	Placebo (N = 60) N	%	p
Headache	12	18.8	9	15.0	.64
Fatigue	9	14.1	7	11.7	.79
Nausea	8	12.5	4	6.7	.37
Flu-like symptoms	7	10.9	4	6.7	.52
Insomnia	6	9.4	1	1.7	.12
Tremor	5	7.8	1	1.7	.21
Skin problems/mild rash	5	7.8	1	1.7	.21
Dizziness	1	1.6	5	8.3	.17
Abdominal pain	4	6.3	3	5.0	> .99
Rash	3	4.7	4	6.7	.71
Joint/muscle pain	2	3.1	4	6.7	.43
Back pain	2	3.1	3	5.0	.67
Agitation	1	1.6	3	5.0	.35

As mentioned before, 1 patient in the lamotrigine group developed a manic episode with psychotic features for which he was hospitalized (SAE). In addition to this patient, 4 patients receiving lamotrigine and 2 patients receiving placebo developed a hypomanic episode (CGI-BP severity of mania = 3). The number of manic or hypomanic switches was not statistically different. Combined response and no switch into mania or hypomania was obtained in 39 patients (60.9%) receiving lamotrigine and 28 patients (46.7%) receiving placebo (p = .149).

DISCUSSION

To our knowledge this is the first randomized controlled trial to assess the efficacy of lamotrigine as add-on

treatment to ongoing lithium therapy in patients with bipolar depression. The results show a clinically significant (> 4 points) difference in favor of lamotrigine on the primary outcome measure (change from baseline in MADRS score) and on several secondary outcome measures, including MADRS scores at weeks 6 and 8, the percentage of MADRS responders at endpoint, and 6 of 10 items on the MADRS, including core depressive symptoms as apparent sadness, reported sadness, inability to feel, and suicidal thoughts. Results obtained with the CGI-BP change of depression were equivocal, with weekly scores and overall response rates numerically favoring lamotrigine but not reaching statistical significance. This could be due to limitations in the sensitivity of the CGI-BP. Another possibility is that this resulted from a more optimistic impression among the physicians when assessing the effect of treatment since start of treatment, compared with the cross-sectionally–assessed MADRS. However, previous lamotrigine studies did show significant change in CGI ratings of depressed bipolar patients.[23–25]

This study indicates efficacy for lamotrigine in the acute treatment of bipolar depression, which complements similar findings in 2 previous studies with lamotrigine monotherapy.[17,23] However, 4 subsequent placebo-controlled trials with lamotrigine monotherapy were all negative, possibly because of high placebo response (35%–47% as assessed by MADRS or HAM-D-17) or lack of intrinsic efficacy,[20] while in another study lamotrigine was less effective but better tolerated than a combination of olanzapine and fluoxetine.[22]

Besides the possibility of a chance effect, there are several possible explanations for our positive finding compared with previous, mostly negative studies. First, this was an add-on study in which all patients received lithium, a treatment that appears to have some efficacy on its own in the treatment of bipolar depression.[30] The combination of lithium and lamotrigine may have produced additive effects, or the efficacy of lamotrigine may have been enhanced by concurrent lithium treatment. Although this might be speculative, the potentially synergic action could come as a result of common final therapeutic pathways involving presynaptic serotonin release and increased neuroplasticity.[31,32] A pharmacokinetic interaction seems unlikely in view of a previously conducted drug interaction study.[33] On the other hand, the add-on design could have reduced the chance of positive findings, since, as a general rule, this type of trial is less likely to be successful in bipolar disorder.[34]

Second, the relatively low overall dropout rate (17.7%) in the current study permitted a robust efficacy assessment due to fewer missing data. Thus, it affirms the utility of add-on study designs in this patient population. The low dropout rate may be attributable to various reasons. First, all patients had the option to get an antidepressant during the second phase of the study, if they should not respond to the study drug at the end of the double-blind trial. Second, there is a difference in health care systems in the countries in which our study was conducted compared to the health care systems in which previous lamotrigine studies[21] were conducted. In the Netherlands and Spain all inhabitants have a mandatory health insurance program that pays for the treatment of bipolar disorder, whereas this is not the case in the United States, where all the negative acute trials were conducted. This means that most patients could stay with their own physician, even during their participation in the trial.

The response to lamotrigine occurred rather late. In 2 recent trials comparing quetiapine with placebo in bipolar depression and in the trial with the combination of olanzapine plus fluoxetine versus placebo, there was a separation between medication and placebo after 1 week.[8,9] In our study, this separation occurred at 6 weeks, which is comparable with the separation at 5 weeks in the prior positive study with lamotrigine monotherapy.[18] This delayed effect of lamotrigine might be due to the slow titration of lamotrigine.

Switch to mania or hypomania occurred in 7 patients: in 5 patients who were taking lamotrigine and in 2 patients taking placebo. Changing mood states form the core feature of bipolar disorder; placebo response is always a factor to consider, especially in rapid cycling patients who typically have frequent episodes of relatively short duration. Although severe rapid cycling (more than 10 episodes in the last year) was an exclusion criterion, nearly 13% of enrolled patients met DSM-IV criteria for rapid cycling (4–9 episodes), which is comparable with the overall frequency (15%) of rapid cycling reported in previous studies.[3] In the quetiapine versus placebo study,[9] 18.2% of the patients were rapid cyclers. In the olanzapine (plus fluoxetine) versus placebo study,[8] more than 35% of the patients were rapid cyclers. Although the rapid cycling patients showed more switches than the non–rapid cycling patients, we did not detect a difference in efficacy, unlike 2 recent studies,[35,36] which indicated a greater short-term response to olanzapine or clozapine in rapid cycling versus non–rapid cycling patients. However, detection of any such difference may have been hampered by lack of statistical power for this subgroup and confounded by a near-significant difference in the incidence of rapid cycling between the lamotrigine and placebo groups.

In this study, the combination of lithium and lamotrigine was well tolerated. There were relatively few serious adverse events for this population and other adverse events were all mild or moderate and did not differ in frequency from placebo. The relatively low rate of skin rash observed in this study may be attributable to slow titration of lamotrigine in accordance with the manufacturer's recommendations and confirms that lithium does not increase the risk of lamotrigine-induced rash.

The most important limitation of our study is the relatively small overall sample size (smaller than initially planned), which did not permit subgroup analyses for assessment of response predictors and moderators. Another limitation is that we have no reliable data regarding the number of bipolar patients in the study centers who developed a depressive episode while being treated with lithium and who were not selected for the study. Finally, we have no sufficient data on patients' recent treatment histories to suggest where the combination of lithium and lamotrigine might fit within treatment algorithms.

Because many bipolar depressed patients do not respond adequately to monotherapy, there is an urgent need for studies addressing the efficacy of other treatment regimens, including combinations with mood stabilizers. Currently published placebo-controlled studies have only addressed the combination of an antidepressant (paroxetine or imipramine) with lithium,[13] of olanzapine plus fluoxetine,[8] and of the addition of an antidepressant to various mood stabilizers and/or atypical antipsychotics.[12] Our study is the first placebo-controlled study that addressed the combination of lamotrigine and lithium in bipolar depression. This combination has been considered interesting, especially since in the 2 long-term studies comparing both lamotrigine and lithium with placebo, lithium was especially effective in the prevention of manic episodes and lamotrigine especially effective in the prevention of depressive episodes.[24,25]

Regarding clinical consequences, several questions remain about the place of the combination of lamotrigine and lithium in the treatment of bipolar depression. Antidepressants remain another possible option in the treatment of bipolar depression in patients using lithium.[8,11,37–39] However, their use may be associated with the risk of a switch to mania or hypomania.[8,11,37–39] Further studies are needed to compare these and other options, such as (combinations with) atypical antipsychotics. Another question is whether the effects of lamotrigine and lithium will be maintained in the responders; this will be addressed in the not yet analyzed, 1-year continuation phase of this study.

Drug names: carbamazepine (Carbatrol, Equetro, and others), clozapine (FazaClo, Clozaril, and others), fluoxetine (Prozac and others), fluoxetine/olanzapine (Symbyax), gabapentin (Neurontin and others), imipramine (Tofranil and others), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), lorazepam (Ativan and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel).

Author contributions: The study was initiated by **Dr. Nolen**, who also designed and wrote the protocol. Data collection was done by all the co-investigators in the LamLit Study Group. Statistical analysis was done by **Dr. Mulder**. Interpretation of the data was done by **Drs. Nolen**, **Mulder**, **Vieta**, and **van der Loos**. All authors commented on and approved the article.

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