Bipolar Disorders 2011: 13: 111–117

BIPOLAR DISORDERS

Brief Report

Long-term outcome of bipolar depressed patients receiving lamotrigine as add-on to lithium with the possibility of the addition of paroxetine in nonresponders: a randomized, placebo-controlled trial with a novel design

van der Loos MLM, Mulder P, Hartong EGThM, Blom MBJ, Vergouwen AC, van Noorden MS, Timmermans MA, Vieta E, Nolen WA, for the LamLit Study Group. Long-term outcome of bipolar depressed patients receiving lamotrigine as add-on to lithium with the possibility of the addition of paroxetine in nonresponders: a randomized, placebo-controlled trial with a novel design.
Bipolar Disord 2011: 13: 111–117. © 2011 The Authors.
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Objective: In two previous manuscripts, we described the efficacy of lamotrigine versus placebo as add-on to lithium (followed by the addition of paroxetine in nonresponders) in the short-term treatment of bipolar depression. In this paper we describe the long-term (68 weeks) outcome of that study.

Methods: A total of 124 bipolar depressed patients receiving lithium were randomized to addition of lamotrigine or placebo. After eight weeks, paroxetine was added to nonresponders for another eight weeks. Responders continued medication and were followed for up to 68 weeks or until a relapse or recurrence of a depressive or manic episode.

Results: After eight weeks, the addition of lamotrigine to lithium was significantly more efficacious than addition of placebo, while after addition of paroxetine in nonresponders both groups further improved with no significant difference between groups at week 16. During follow-up the efficacy of lamotrigine was maintained: time to relapse or recurrence was longer for the lamotrigine group [median time 10.0 months (confidence interval: 1.1–18.8)] versus the placebo group [3.5 months (confidence interval: 0.7–7.0)].

Conclusion: In patients with bipolar depression, despite continued use of lithium, addition of lamotrigine revealed a continued benefit compared to placebo throughout the entire study.

Disclosure information for all authors is listed before the references.

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doi: 10.1111/j.1399-5618.2011.00887.x

Key words: bipolar disorders – lamotrigine – lithium

Received 4 May 2010, revised and accepted for publication 3 December 2010

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This study protocol is registered at:
http://www.ClinicalTrials.gov: ClinicalTrials.gov Identifier: NCT00224510.

Bipolar disorders are characterized by recurrent mood episodes. While 98% of patients achieve syndromatic recovery from an acute manic or depressive episode within two years (1), 80–90% of patients suffer from new episodes thereafter (1–3). Despite the use of mood stabilizers such as lithium or valproate, especially depressive episodes and days with depressive symptoms are frequent and may prove difficult to treat (2, 4, 5). Lithium and perhaps to a lesser extent valproate have some but limited efficacy in the treatment and prevention of depressive episodes (6–8). There is a controversy regarding the use of antidepressants, both in the treatment of acute depressive episodes (9, 10) as well as in long-term treatment of bipolar disorder (11–13). Of the atypical antipsychotics, only quetiapine (14–17) and olanzapine (especially in combination with fluoxetine) (18) demonstrated efficacy in acute bipolar depression. Moreover, olanzapine (19) and quetiapine (as add-on to lithium or valproate) (20, 21) were found effective in the prevention of depressive recurrences.

Another treatment option for bipolar depression is lamotrigine. The results from the acute studies in bipolar depression are contradictory. The first randomized, controlled trial (RCT) found a significant difference between lamotrigine and placebo in favour of lamotrigine, although only on secondary outcome measures (22). Four additional RCTs thereafter found no difference between lamotrigine monotherapy and placebo, probably because of a high placebo response in these studies (23, 24). Nevertheless, in a meta-analysis of all five studies, lamotrigine was more effective than placebo (25). In addition, lamotrigine has been compared with placebo and lithium in long-term treatment of bipolar disorder. In two studies (26, 27) lamotrigine was found effective in preventing depressive recurrences, while lithium was effective in preventing manic recurrences.

In two previous papers, we described the short-term results of a placebo-controlled RCT investigating the effects of the addition of lamotrigine to lithium in patients with bipolar depression despite long-term treatment with lithium. In the first phase of that study (weeks 1–8), lamotrigine was found to be more effective than placebo (28); in the second phase (weeks 9–16), further addition of paroxetine in nonresponders to either lamotrigine or placebo (plus lithium) was associated with further improvement in both groups, while the difference between lamotrigine and placebo was no longer significant at week 16 (29). In this paper, we describe the results of the long-term outcome of that study.

Methods

Study design

In this paper, we describe the follow-up of an investigator (WAN)-initiated, randomized, double-blind, placebo-controlled trial with three phases. The design of the study is shown in Figure 1 and has been described in detail elsewhere (28, 29).

During the first eight weeks of the study (phase 1), 124 patients with a bipolar I or II disorder and a depressive episode with ≥ 18 points on the Montgomery-Åsberg Depression Rating Scale (MADRS) (30) despite long-term treatment with lithium received lamotrigine or placebo in addition to ongoing treatment with lithium (28). Nonresponders (n = 37) to the addition of either lamotrigine or placebo at week 8 were offered the opportunity to receive further addition of paroxetine (open label) in combination with ongoing lithium plus lamotrigine or placebo during weeks 9–16 (phase 2) (29).

Responders at 8 or 16 weeks were followed until maximally week 68 (phase 3) or until they reached the primary endpoint (a depressive or manic relapse or recurrence). The medication regime (lithium, double-blind lamotrigine or placebo, and in some patients paroxetine as well) was kept stable during the entire follow-up. Patients who left the study without a relapse or recurrence were considered dropouts; reasons for dropout were recorded.

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.

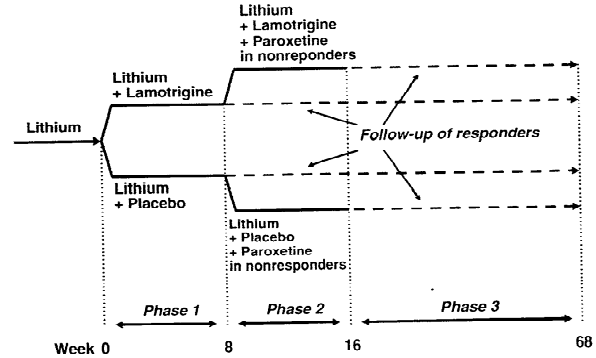

Fig. 1. Design of the study.

Treatments

All patients were already receiving lithium, which was maintained at a plasma level of 0.6–1.2 mmol/L throughout the study. During phase 1, lamotrigine (or placebo in identical tablets) was up-titrated to 200 mg/day at week 6 and maintained at this dose throughout the study. In nonresponders, at week 8 paroxetine was started at 20 mg/day and also maintained at this dose throughout the study. In addition to the study medication (lithium, lamotrigine or placebo, and paroxetine) patients were not allowed to take other psychotropic drugs, with the exception of benzodiazepines at a maximum of 2 mg lorazepam equivalents/day.

Assessments and outcome measures

After baseline, patients were seen every two weeks until the end of phase 2 (week 16). During follow-up (phase 3), patients were assessed at week 20 and thereafter every two months. During all visits, patients were scored on the MADRS and the Clinical Global Impression–Bipolar version (CGI-BP) (31); adverse events and study medication compliance were also assessed. Lithium plasma levels were measured every four months.

Response during phase 1 and 2 leading to follow-up was defined as a score of 1 or 2 (very much or much improved) according to the CGI-BP improvement of depression scale. Outcome of the study was the relapse or recurrence of a manic or depressive episode defined as a score ≥ 4 (at least moderate symptoms) on the CGI-BP severity of depression or mania scale. In addition, it was investigated how long the MADRS score was maintained at $< 50\%$ of its baseline value after patients reached this level for the first time during phase 1 or 2.

Statistics

All analyses concerning efficacy during follow-up (phase 3) have to be considered in a descriptive sense without statistical testing. This is because the groups entering follow-up were selected by the treatment-dependent outcome '(very) much improvement of depression on the CGI-BP' and consequently had become formally incomparable at this stage.

The evolution of no symptoms or only mild symptoms (both CGI-BP mania and depression severity score < 4) during the whole study was described by calculating percentages with no or only mild symptoms of the original group sizes at each visit. In addition, the sustainability of a MADRS score $< 50\%$ of baseline after the first attainment of this level was compared between the two treatment groups using a Kaplan–Meier survival analysis.

The frequencies of the various types of adverse events occurring in more than 5% of the patients during the continuation phase were compared between the two treatment groups using a chi-square trend test.

Results

Patient characteristics at baseline are presented in Table 1. Treatment groups were balanced at baseline, considering the uniform distribution of p-values over the interval (0.1). The flowchart of the study, including reasons for dropping out during the three phases, is presented in Figure 2.

In phase 1, a total of 124 patients were randomized to lamotrigine (n = 64) or placebo (n = 60); 102 completed this phase. After eight weeks, the difference in change of MADRS score (the primary outcome criterion during phase 1) was significant [−15.37 versus −11.16, respectively (p = 0.029)] (28).

In phase 2, nonresponders to lamotrigine (n = 9) or placebo (n = 18) received addition of paroxetine (phase 2). At the end of phase 2, both groups were further improved, while the difference between groups in change of MADRS score was no longer significant [−17.91 for the lithium–lamotrigine–paroxetine algorithm versus −15.40 (p = 0.253) for the lithium–placebo–paroxetine algorithm] (29).

Lithium plasma levels were measured at baseline and at weeks 8, 16, 32, 48, and 64. The overall variation in mean plasma levels was 0.73–0.82 mmol/L for the lamotrigine group versus 0.72–0.83 mmol/L for the placebo group.

Long-term efficacy

Responders, according to the CGI-BP, during either phase 1 or phase 2 were eligible for follow-up. At each visit during follow-up, the number of patients who maintained responder status (CGI-BP severity of depression or mania score < 4) was calculated as percentage of the group who started with either lamotrigine or placebo in phase 1. These percentages maintained higher levels in the lamotrigine group than in the placebo group throughout the study (Fig. 3). No formal statistical test was done here because of the selected group for follow-up (see Methods). The drop in percentage between weeks 16 and 20 is caused by the

Table 1. Patient and illness characteristics at study entry

	Lamotrigine (n = 64)	Placebo (n = 60)	Total (n = 124)	Statistic	Value	df	p-value
Female gender, n (%)	37 (57.8)	30 (50.0)	67 (54.0)	Fisher's	–	–	0.471
Age, years, mean (SD)	45.2 (12.1)	47.6 (11.6)	46.4 (11.9)	*t*-test	1.13	122	0.261
Illness characteristics							
Bipolar I disorder, n (%)	43 (67.2)	41 (68.3)	84 (67.7)	Fisher's	–	–	1.000
Rapid cycling course, last 12 months, n (%)	12 (18.8)	4 (6.7)	16 (12.9)	Fisher's	–	–	0.061
MADRS score, mean (SD)	28.25 (5.97)	28.82 (6.24)	28.52 (6.08)	*t*-test	0.52	122	0.606
CGI-BP depression severity score, mean (SD)	4.56 (0.64)	4.53 (0.57)	4.55 (0.60)	Chi sq. trend	0.07	1	0.882
CGI-BP mania severity score, mean (SD)	1.03 (0.18)	1.03 (0.18)	1.03 (0.18)	Fisher's	–	–	1.000
Lithium plasma level at baseline, mmol/L, mean (SD)	0.82 (0.16)	0.84 (0.16)	0.83 (0.16)	*t*-test	0.48	122	0.634
Previous other treatments for index depressive episode, n (%)							
TCA	6 (9.4)	4 (6.7)	10 (8.1)	Fisher's	–	–	0.745
SSRI/SNRI	15 (23.4)	16 (26.7)	31 (25.0)	Fisher's	–	–	0.836
MAOI	1 (1.6)	3 (5.0)	4 (3.2)	Fisher's	–	–	0.353
Antipsychotic, typical	4 (6.3)	3 (5.0)	7 (5.6)	Fisher's	–	–	1.000
Antipsychotic, atypical	15 (23.4)	11 (18.3)	26 (21.0)	Fisher's	–	–	0.317
Valproic acid	5 (7.8)	2 (3.3)	7 (5.6)	Fisher's	–	–	0.247
Carbamazepine	1 (1.6)	3 (5.0)	4 (3.2)	Fisher's	–	–	0.285
Benzodiazepine	44 (68.8)	35 (58.3)	79 (63.7)	Fisher's	–	–	0.154
Other	3 (4.7)	4 (6.7)	7 (5.6)	Fisher's	–	–	0.464

MADRS = Montgomery-Åsberg Depression Rating Scale; CGI-BP = Clinical Global Impression–Bipolar version; TCA = tricyclic antidepressants; SSRI = selective serotonin reuptake inhibitors; SNRI = serotonin-norepinephrine reuptake inhibitors; MAOI = monoamine oxidase inhibitors.

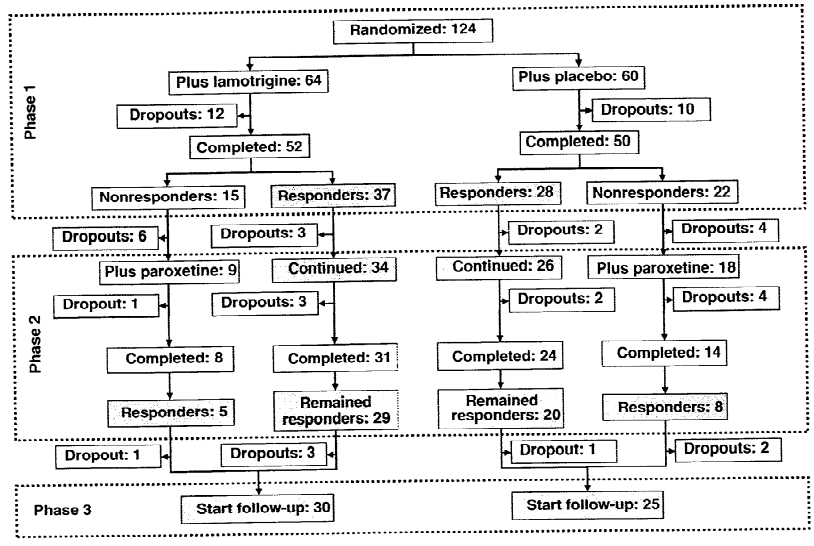

Fig. 2. Flow chart of the study.

treatment-dependent selection of patients entering follow-up.

We also calculated time to first relapse or recurrence based on the MADRS score after having achieved responder status according to the MADRS (i.e., < 50% of baseline) for the first time during phase 1 or phase 2. In this analysis, patients who left the study for any reason were censored.

The time to relapse or recurrence was longer for the lamotrigine group than for the placebo group: median time 10.0 months [95% confidence interval (CI): 1.1 18.8] versus 3.5 months (95% CI:

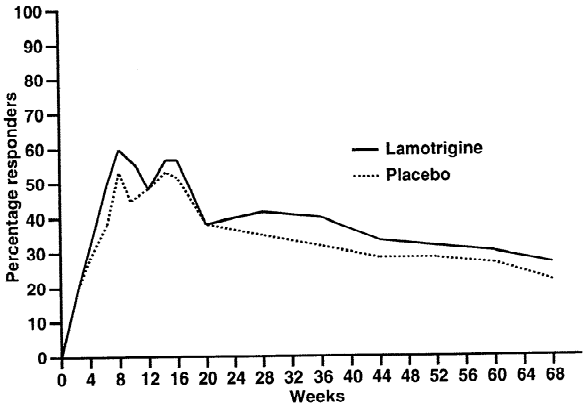

Fig. 3. Responders (Clinical Global Impression–Bipolar version improvement of depression score of 1 or 2) as percentage of the initial group (N = 124; lamotrigine n = 64, placebo n = 60) throughout all three phases of the study.

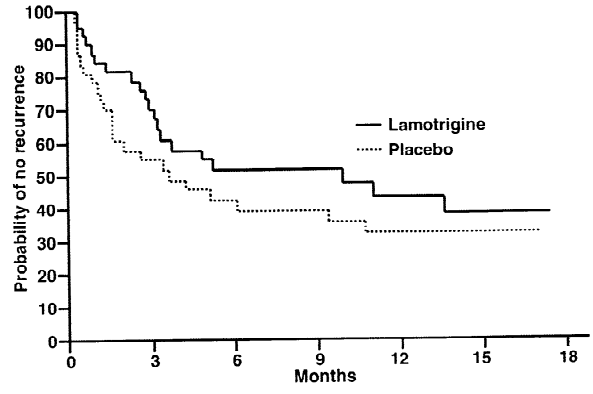

Fig. 4. Probability of maintaining response [score < 50% of Montgomery-Åsberg Depression Rating Scale (MADRS) score at baseline] without recurrence (score ≥ 50% of initial MADRS) after having achieved responder status for the first time during phase 1 or phase 2. Median time to relapse or recurrence for the lamotrigine group was 10.0 months (95% confidence interval: 1.1–18.8) versus 3.5 months (95% confidence interval: 0.7–7.0) for the placebo group.

0.7–7.0), respectively (see Fig. 4). No formal statistical test was performed.

At the end of the study (68 weeks), 18 patients (28.1%) from the lamotrigine group were still in the study versus 14 patients from the placebo group (23.3%).

Safety

Occurrence of severe adverse events (SAEs) and any adverse events (AEs) during the first 16 weeks of this study were described in detail previously (28, 29). During follow-up, 5 SAEs were observed: 2 in the lamotrigine group (1 patient developed an atrial flutter and 1 had high blood pressure), and 3 in the placebo group (2 patients had a severe depressive recurrence and 1 a urinary tract infection). None of the SAEs were considered to be related to study medication and all patients recovered. The AEs occurring in more than 5% of any group are listed in Table 2. There was no difference between lamotrigine and placebo in the prevalence of any AE. The total amount of AEs in both groups was remarkably low for a 68-week follow-up.

Table 2. Adverse events occurring in ≥ 5% of patients in any group (linear-by-linear association, two-sided)

	Lamotrigine (n = 30)	Placebo (n = 25)	p-value
Pulmonary problems	3 (10.0)	0 (0)	0.242
Blurred vision	2 (6.7)	0 (0)	0.495
Hallucinations	2 (6.7)	0 (0)	0.495
Throat problems	3 (10.0)	2 (8.0)	0.383
Joint/muscle pain	2 (6.7)	3 (12.0)	0.1000
Headache	3 (10.0)	2 (8.0)	0.383
Nausea	4 (13.3)	1 (4.0)	0.301
Flu-like symptoms	3 (10.0)	1 (4.0)	0.492
Insomnia	3 (10.0)	2 (8.0)	0.745
Abdominal pain	3 (10.0)	0 (0)	0.242
Hypertension	2 (6.7)	0 (0)	0.495
Back pain	1 (3.3)	2 (8.0)	0.585
Coordination problems	2 (6.7)	0 (0)	0.495
Eye problems	2 (6.7)	0 (0)	0.495

Values are reported as n (%).

Five patients in the lamotrigine group and 8 patients in the placebo group developed a (hypo)manic episode during follow-up.

Discussion

In this paper, we describe the long-term follow-up of an RCT consisting of three phases. With this quite novel design we were able to compare two different treatment algorithms, one with lamotrigine added to lithium and one with placebo added to lithium (phase 1), both followed by addition of paroxetine in nonresponders (phase 2) and a subsequent follow-up in responders after phase 1 or 2 (phase 3). We found that the algorithm with lamotrigine addition was not only more effective than the algorithm with placebo addition in the acute treatment of bipolar depression but also appeared to retain its efficacy throughout the entire study. The percentage of responders as well as the time to relapse after initial response was favourable for the lamotrigine group versus the placebo group.

In our opinion, the design of our study has several advantages and disadvantages. The first advantage is that the add-on design closely resembles real life, in which many bipolar disorder patients receive

multiple medications rather than monotherapy (32–34). In addition to the usual design of an RCT comparing lamotrigine or placebo added to lithium, we also could provide data on the addition of a third drug (paroxetine) to lithium and lamotrigine (or placebo) and on the long-term follow-up. Thus, our study provides useful information on the efficacy and safety of adjunctive lamotrigine compared to placebo in the acute as well as the long-term treatment of bipolar depression.

A second advantage is that nonresponders after phase 1 could receive active medication (paroxetine) in phase 2, thus increasing the feasibility of the study. We hypothesize that it may also partly explain the relative low dropout rate in our study (only 38% during the first two phases and 74% over the entire study of 68 weeks), which is much lower than in the two previous long-term trials with lamotrigine (26, 27). In these studies, 98% and 85% of those who were randomized to lamotrigine or placebo, respectively, were dropouts after 68 weeks.

The main disadvantage of this design is that the selection of nonresponders for receiving paroxetine after phase 1 and the selection of responders after phase 1 and 2 for continuation of the study led to an unequal number of patients leaving the study at these decision points. This eventually hampered possibilities for an analysis with statistical testing of the results of phase 3.

The main limitation of our study is the relatively small sample size. This was already a problem in the analysis of phase 1, in which 124 patients participated while the study was originally planned to recruit 220 patients, and it definitely hampered statistical analysis after phase 2. Thus, our findings must be interpreted with some caution.

Nevertheless, we conclude that lamotrigine was more effective than placebo as add-on treatment to lithium in patients with breakthrough bipolar depression and was well tolerated in combination with lithium. Moreover, lamotrigine could safely be combined not only with lithium but also with paroxetine and appeared to retain its efficacy and good tolerability throughout follow-up.

Acknowledgements

This study was supported by GlaxoSmithKline, Zeist, and the Isala Klinieken, Zwolle, The Netherlands. The study was initiated by Willem Nolen, who also designed and wrote the protocol. Data collection was carried out by all of the co-investigators in the LamLit Study Group. GSK provided lamotrigine and placebo as well as the randomisation list. Study monitoring was performed by GSK Netherlands and GSK Spain. Statistical analysis was done by Paul Mulder. Interpretation of the data was done by Willem Nolen, Paul Mulder, Eduard Vieta, and Marc van der Loos. All authors commented on and approved the manuscript.

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Disclosures

MLMvdL has served as an advisor or speaker for AstraZeneca and Bristol-Myers Squibb; his employer, The Isala Klinieken, was compensated by GlaxoSmithKline for his time spent on this manuscript. PM's employer, The Department of Biostatistics, Erasmus Universtiy Medical Center, Rotterdam, was compensated by GlaxoSmithKline for his time spent on this manuscript. EGThMH has served as an advisor or speaker for AstraZeneca, Bristol-Myers Squibb, and GlaxoSmithKline. ACV has received a research grant from GlaxoSmithKline; and has served as a speaker or advisor for Eli Lilly & Co., Wyeth, and Lundbeck. MAT was an employee of GlaxoSmithKline until June, 2008. EV has received grants, and served as a consultant, advisor, or speaker for Almirall, AstraZeneca, Bristol-Myers Squibb, Eli Lilly & Co., Forest Research Institute, Geodon Richter, GlaxoSmithKline, Janssen-Cilag, Jazz, Lundbeck, Merck, Novartis, Organon, Otsuka, Pfizer, Pierre-Fabre, Qualigen, Sanofi-aventis, Servier, Shering-Plough, Solvay, Takeda, The Spanish Ministry of Science and Innovation (CIBERSAM), The Seventh European Framework Programme (ENBREC), the Stanley Medical Research Institute, United Biosource Corp., and Wyeth. WAN has received grants from the Netherlands Organisation for Health Research and Development, the European Union, the Stanley Medical Research Institute, AstraZeneca, Eli Lilly & Co., GlaxoSmithKline, and Wyeth; has received honoraria/speakers fees from AstraZeneca, Pfizer, Servier, and Wyeth; and has served on advisory boards for AstraZeneca, Pfizer, and Servier. MBJB and MSvN have no conflicts of interest to report.

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