

Research Article



Comparative Study of Efficacy, Safety and Tolerability of Lamotrigine versus Levetiracetam in the Continuous Maintenance Phase of Patients with Bipolar Depressive Disorder

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ABSTRACT

Bipolar disorder, also known as manic-depression, is a mental illness which causes extreme mood swings between mania (excessive euphoria) and depression. The objective of this study is to evaluate the spectrum of efficacy of Lamotrigine versus Levetiracetam as add on therapy comparatively in patient with bipolar depressive disorder who are inadequately responsive to or intolerant of pharmacotherapy with conventional drugs at Jabalpur and adjoining area. In this 60 days open label, randomized comparative study 60 patients were enrolled, out of which 53 patients were evaluated at the end of the study. Two parallel groups were differentiated by the study medication—Lamotrigine or Levetiracetam—that was administered as an adjunct to existing medications for bipolar depressive disorder (N=60). At baseline and every 15th days Mood symptoms were rated using the Hamilton depression scale and the Clinical Global Impression (CGI) scale was used to measure overall clinical improvement at each visit. Tolerability was assessed throughout the study via patient-reported and investigator-observed adverse events by a standard verbal probe. Total 61% patients in Lamotrigine group had shown marked improvement on HAM-D (>50% reduction on day 60) while 33% patients in Levetiracetam group showed this level of improvement. On CGI-S clinically meaningful improvement (> 2 point decrease) was observed in 92.3% patients in Lamotrigine group, while 51.8% in Levetiracetam group. On comparison between these two drugs on the basis of HAM-D and CGI-S the difference was statistically significant (P value for HAM-D < 0.05 and for CGI-S < 0.025). The addition of either Lamotrigine or Levetiracetam to patients preexisting mood stabilizing regimen was associated with a reduction in the frequency of mood fluctuation. Evidence from this preliminary open-label study suggests that Lamotrigine was efficacious than Levetiracetam in reducing depressive symptoms in patients presenting with depressive phases of bipolar I and bipolar II disorder. Lamotrigine and Levetiracetam were well tolerated, with adverse-event profiles and the most common adverse events in both treatment groups were Dizziness, Headache and Somnolence.

Keywords: Bipolar disorder, Lamotrigine, Levetiracetam.

INTRODUCTION

Bipolar disorder, also known as manic-depression, is a mental illness which causes extreme mood swings between mania (excessive euphoria) and depression, negatively impacting an individual's ability to function normally.¹ According to a new report in the March issue of the Archives of General Psychiatry the Worldwide prevalence of bipolar disorder type I is estimated to be 0.6%, that of type II is 0.4%, and that of sub threshold Bipolar disorder is 1.4%, yielding a total bipolar disorder spectrum prevalence of 2.4% (2). Sufferers are at a 30-times greater risk of committing suicide than the general population, which makes accurate diagnosis and effective treatment a priority.¹⁻³ Bipolar disorder is defined, by The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*⁴, as recurrent episodes of depression and mania.

The objective in the psychopharmacologic treatment of bipolar disorder is the maintenance of euthymia through the prevention of cycling. Many patients require complex combinations of mood stabilizers with various

psychotropic's (e.g., antidepressants, antipsychotics, benzodiazepines) for optimal stabilization.

At present, a broad-spectrum medication that is effective in all phases of the illness and that can be used in monotherapy is not available. Lithium, Valproate, and carbamazepine possess moderate to marked antimanic properties; data suggest that Valproate is more effective than lithium in mixed states. However, all three agents are typically less effective in the treatment of depression. This is an important clinical problem; since there is increased morbidity and mortality associated with the depressed and mixed phases of bipolar disorder. With increasing data demonstrating that depression is the dominant pole in bipolar disorder (1,3), and with the emergence of Lamotrigine as the first mood stabilizer with better efficacy at either treating or preventing depression than mania, research on optimal treatments for bipolar depression has been increasing.

Lamotrigine has emerged with a distinct place in the pharmacological treatment of bipolar disorder, with the potential to treat and prevent bipolar depression, which is the dominant and arguably most disabling and under-treated phase of the illness. The data supports its



tolerability and safety, the strongest evidence for its efficacy lies in the prevention of bipolar depression.

Levetiracetam is an anti convulsant drug that was recently approved by FDA for use in epilepsy and is currently under investigation for use in bipolar disorder.

Aim and Objective

1. To study efficacy of Lamotrigine in treatment of Bipolar Depressive Disorder.
2. To study & compare efficacy of Levetiracetam with Lamotrigine in treatment of Bipolar Depressive Disorder.
3. To study & compare the tolerability (side effects) of Lamotrigine & Levetiracetam in the treatment of Bipolar Depressive Disorder.

MATERIALS AND METHODS

Study Area and Study Design

The protocol for this randomized, open label, parallel-group study was performed at the Department of psychiatry NSCB Medical College Jabalpur (MP) where patients are offered out patient's consultation and approved by an institutional review board.

Selection Criteria

Sample size

The duration of study was of one year. The patients were 60 outpatients with bipolar disorder. (Type I, N= 36; Type II, N= 24), diagnosed by means of the Structured Clinical Interview for Axis I DSM-IV Disorders. Each Patient was undergoing detailed psychiatric neurological & medical examination.

Inclusion Criteria

1. Patients were at least age of 18 years.
2. They should had a depressive episode despite being treated with one mood stabilizers (lithium, Divalproexetc) for at least 3 months at therapeutic doses as determined by the clinician /investigator.
3. Patients with two consecutive weekly ratings on the Hamilton depression scale (5) of at least 16, a Clinical Global Impression scale for Bipolar Disorder depression severity score of at least 3.
4. Should be able to communicate in Hindi/ English.

Exclusion Criteria

1. Patient who showed clinically relevant levels of mania- a Young Mania Rating scale (6) score of at least 14 or 1.
2. CGI-BP mania severity score of at least 3 (suggesting clinically meaningful mania) at base line or at any point of study were excluded from the study.
3. Patients with a history of epilepsy.

4. Associated psychotic illness or rapid cycler, active suicidality.
5. Clinically significant medical illness.
6. Pregnant/Nursing females.
7. History of prior treatment or hypersensitivity with Lamotrigine/ Levetiracetam.
8. Unable to provide informed consent.
9. History of alcohol or substance dependence within the past year was excluded.

Procedures

The study comprised a less than 1-week screening phase, and 6-week escalation phase (weeks 1 to 6), and a 3-week maintenance phase (weeks 7 to 9). Clinic visits occurred at screening; baseline (Week 0); and on days 15th, 30th, 45th, and 60th.

Two parallel groups were differentiated by the study medication—Lamotrigine or Levetiracetam—that was administered as an adjunct to existing medications for bipolar depressive disorder (N=60). Patients determined during the screening phase to meet entry criteria were randomized 1:1 to receive Lamotrigine or Levetiracetam at the baseline visit. After a complete description of the study, written informed consent was obtained from all subjects.

The patients, who were on lithium therapy and were supposed to receive Lamotrigine, were started with 50 mg/d and the dose was escalated to a maximum of 300 mg/day. If the patients were on carbamazepine therapy then, they were started with 100 mg/d and the dose was escalated to a maximum of 400 mg/d. If the patients were on divalproex therapy then, they were started with 25 mg/d and the dose was escalated to a maximum of 200 mg/d. The dose escalation was in a flexible manner on the basis of response and on the advice of the psychiatrist.

While Levetiracetam was started with 500 mg/d and dose was escalated to a maximum of 2000 mg/d in a flexible manner in all patients irrespective of their mood stabilizing drugs.

On the basis of the presence of concomitant anticonvulsant enzyme inducers such as Carbamazepine or enzyme inhibitors such as Valproate, three Lamotrigine dosing schedules, including both once-daily and twice-daily regimens, were used in order to provide similar Lamotrigine plasma concentrations and reduce the risk of rash across the three dosing groups.

Laboratory parameters (SGOT, SGPT) were also investigated at Baseline and day 30th and 60th to assess adverse effects.

Measure / Response

At baseline and every 15th days Mood symptoms were rated using the Hamilton depression scale and the Clinical



Global Impression (CGI) scale was used to measure overall clinical improvement at each visit.⁷

Statistical analyses

Statistical analyses consisted of descriptive statistics and paired t tests for baseline (days 0) measures compared with the last observation.

The primary health outcomes end point was the change between baseline and the end of the maintenance phase in the 17-item Hamilton depression scale. Responder analysis was also performed.

- Marked improvement was defined as a 50% or greater decrease in score from baseline to endpoint on the first 17 items of the Hamilton depression scale, Moderate improvement was defined as a 26%–49% decrease in these scores or a decrease in the CGI-BP depression score of at least 2 points (clinically meaningful improvement).
- Remission criteria included a 17 items of the Hamilton depression scale below 7 and/or a CGI-BP depression severity score of 1 (normal, not ill) at study endpoint.

Tolerability assessment

Tolerability was assessed throughout the study via patient-reported and investigator-observed adverse events by a standard verbal probe. An adverse event was defined as any untoward medical occurrence regardless of cause.

First 17 items of the Hamilton depression scale (5)

This is the one of the earliest scales to be developed for depression, and is a clinician rated scale aimed at assessing depression severity among patients. The 17-item version of the HAM-D is the standard for clinical trials in depression and, over the years, the most widely used scale for controlled clinical trial in depression.

The HAM –D is a multidimensional scale, it shows the internal consistency of 0.83 and high inter-reliability of >0.60. It is accepted by most clinician that scores between 0 and 6 do not indicate the presence of depression, score between 7 and 17 indicate mild depression, scores between 18 and 24 indicate moderate depression, and scores over 24 indicate severe depression. A total HAM-D score of 7 or less after treatment is for most rater a typical indicator of remission, a decrease of 50% or more from base line during the course of the treatment is considered indicator of clinical response, or in other words, a clinically significant change.

RESULTS

In our study total number of patients recruited was 60 (Male = 47 and Female =13). Total 36.66% patients were in the age group of 20-30 year. Bipolar disorder is more common in younger people. The Mean age was 34.2 (± 10.36). Total seven patients were dropped out during the study.

Table 1: Age & Gender Wise Distribution

Age	Male (Strength)	%	Female (Strength)	%	Total (Strength)	%
<20	2	4.255	0	0	2	3.333
20-29	17	36.17	5	38.461	22	36.666
30-39	16	34.04	3	23.076	19	31.666
40-49	7	14.893	5	38.46	12	20
50+	5	10.638	0	0	5	8.333
Total	47	100	13	100	60	100

Efficacy of Lamotrigine Group

Table 2: Mean Ham-D Scores

Days	Ham – D Score (mean \pm S.D)
Day 0	21.07 \pm 2.96
Day 15	18.27 \pm 2.88
Day 30	14.85 \pm 2.77
Day 45	12.38 \pm 3.24
Day 60	10.35 \pm 4.16

This table shows HAM- D scores comparisons of 15th, 30th, 45th, and 60th day with the day 0 (i. e. baseline) in patients of Lamotrigine group. The mean baseline HAM-D score was 21.07 (± 2.96), which dipped to 10.35(± 4.16) at the end of study. ($p < 0.001$)

Table 3: Change in Ham-D Score

Reduction in ham-D score	No. of Patients (n=26)
>50%	16
\leq 50%	10

Total 61.5% patient's had shown marked improvement HAM-D at day 60.

Table 4: Mean CGI-S Score

Days	CGI-S Score (mean \pm S.D)
Day 0	4.50 \pm 0.82
Day 15	3.86 \pm 0.64
Day 30	3.15 \pm 0.72
Day 45	2.58 \pm 0.76
Day 60	2.08 \pm 0.84



This table shows CGI-SEVERITY scores comparisons of 15th, 30th, 45th, and 60th day with the day 0 (i. e. baseline) in Lamotrigine group. The mean baseline CGI-SEVERITY score was 4.50 (± 0.82), which dipped to 2.08(± 0.84) at the end of study. ($p < 0.001$).

Table 5: Change in CGI-S Score

Reduction In CGI-S Score	No. of Patients (n=26)
≥ 2 Points	24
<2 Points	2

Total 92.3% patients had shown clinically meaningful improvement on CGI- SEVERITY.

Efficacy of Levetiracetam Group

Table 6: Mean HAM-D Score

Days	HAM – D Score (mean \pm S.D)
Day 0	21.30 \pm 3.80
Day 15	18.86 \pm 3.67
Day 30	17.07 \pm 4.21
Day 45	15.78 \pm 4.46
Day 60	13.81 \pm 5.16

This table shows HAM- D scores comparisons of 15th, 30th, 45th, and 60th day with the day 0 (i. e. baseline) of Levetiracetam group. The mean baseline HAM-D score was 21.07 (± 2.96), which dipped to 10.35(± 4.16) at the end of study. ($p < 0.001$)

Table 7: Change in Ham-D Score

Reduction In Ham-D Score	No. of Patients (n=27)
>50%	9
$\leq 50\%$	18

Total 61.5% patient's had shown marked improvement HAM-D at day 60.

Table 8: Mean CGI-S Score

Days	CGI-S Score (mean \pm S.D)
Day 0	4.57 \pm 0.97
Day 15	4.0 \pm 0.86
Day 30	3.86 \pm 0.70
Day 45	3.33 \pm 0.92
Day 60	2.78 \pm 1.22

This table shows CGI-Severity scores comparisons of 15th, 30th, 45th, and 60th day with the day 0 (i. e. baseline) in Levetiracetam group. The mean baseline CGI-Severity score was 4.57 (± 0.97), which dipped to 2.78 (± 1.22) at the end of study. ($p < 0.001$)

Table 9: Change in CGI-S Score

Reduction In CGI-S Score	No. of Patients (n=26)
≥ 2 Points	14
<2 Points	13

Total 92.3% patient's had shown clinically meaningful improvement on CGI- SEVERITY.

Table 10: Comparison of Lamotrigine and Levetiracetam on Ham-D & CGI-Severity Scale

	Lamotrigine (n=26)				Levetiracetam (n=27)			
	Reduction in ham-d		Reduction in CGI-S		Reduction in HAM-D		Reduction in CGI-S	
	>50 %	≤ 50 %	≥ 2 Poin ts	<2 Poin ts	>50 %	≤ 50 %	≥ 2 Poin ts	<2 Poin ts
No. Of patients	16	10	24	2	9	18	14	13

Out of 26 patients in Lamotrigine group 16 patients were shown > 50% (marked) improvement, while in Levetiracetam group 9 patients were improved out of 27 patients. On CGI –S scale total 24 patients in Lamotrigine group and 14 patients in Levetiracetam group were shown clinically meaningful improvement.

On comparison between these two drugs on the basis of HAM-D and CGI-S the difference was statistically significant (P value for HAM-D < 0.05 and for CGI-S< 0.025).

Table 11: Adverse Effects

Side Effects	Lamotrigine		Levetiracetam	
	N=27	%	N=27	%
Dizziness	8	30.76	10	37.03
Headache	7	27	5	18.5
Somnolence	5	19.20	6	22.5
Nausea/ Vomiting	4	15.3	3	11
Fatigue	3	11.5	2	7.4
Insomnia	3	11.5	1	3.7
Nasopharyngitis Pharyngolaryngeal pain	2	7.6	1	3.7
Rash	1	3.8	0	0
Irritability	1	3.8	2	7.4
Tremor	1	3.8	0	0

This table shows the most common side effects were dizziness, headache and somnolence in both treatment groups.

DISCUSSION

In this 60 days open label, randomized comparative study 60 patients were enrolled, out of which 53 patients were evaluated at the end of the study (26 patients in Lamotrigine group and 27 patients in Levetiracetam group).The patients were followed up after every 15 days by using HAM-D and CGI-S.

Total 61% patients in Lamotrigine group had shown marked improvement on HAM-D (>50% reduction on day 60) while 33% patients in Levetiracetam group showed this level of improvement. On CGI-S clinically meaningful improvement (> 2 point decrease) was observed in 92.3%



patients in Lamotrigine group, while 51.8% in Levetiracetam group.

On comparison between these two drugs on the basis of HAM-D and CGI-S the difference was statistically significant (P value for HAM-D < 0.05 and for CGI-S < 0.025).

The improvement in depression with Lamotrigine in this study correlates previous research showing that the drug can enhance mood in patients with bipolar disorder and has mood-stabilizing effects in bipolar disorder.

Calabrese *et al.*,⁸ double-blind controlled study of Lamotrigine monotherapy in bipolar I depression demonstrated significant antidepressant efficacy (Lamotrigine: 51% vs placebo: 26%, $p < 0.05$) on the 17-item HAM-D and CGI-S compared with placebo. Barbosa and colleagues⁹ found that Lamotrigine was superior to placebo in treating major depressive episodes (Lamotrigine 100 mg/day: 85% vs placebo: 30%; $P < 0.05$).

CONCLUSION

The addition of either Lamotrigine or Levetiracetam to patients preexisting mood stabilizing regimen was associated with a reduction in the frequency of mood fluctuation.

Evidence from this preliminary open-label study suggests that Lamotrigine was efficacious than Levetiracetam in reducing depressive symptoms in patients presenting with depressive phases of bipolar I and bipolar II disorder.

Lamotrigine and Levetiracetam were well tolerated, with adverse-event profiles, the most common adverse events in both treatment groups were Dizziness, Headache and Somnolence in both treatment groups.

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