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# A COMPARATIVE STUDY OF EFFICACY OF LAMOTRIGINE AND LEVETIRACETAM IN THE CONTINUOUS MAINTENANCE PHASE OF PATIENTS WITH BIPOLAR DEPRESSIVE DISORDER

**Daryani KK[1]*, Narendra Kumar Bokade[1] and OP Raichandani[2]**
[1]Department of Pharmacology, NSCB Medical College, Jabalpur, India.
[2]Department of Psychiatry, NSCB Medical College, Jabalpur, India.

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**Abstract:** Bipolar disorder, or manic-depressive illness (MDI), is one of the most common, severe, and persistent mental illnesses. Bipolar disorder is a serious lifelong struggle and challenge 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. 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 comparison between these two drugs on the basis of HAM-D the difference was statistically significant (P value for HAM-D < 0.05). 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 more efficacious than Levetiracetam in reducing depressive symptoms in patients presenting with depressive phases of bipolar I and bipolar II disorder.

**Key Words:** Bipolar disorder, Lamotrigin, Levetiracetam

## INTRODUCTION

Bipolar disorder is defined, by The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) [1], as recurrent episodes of depression and mania. Bipolar disorder, or manic-depressive illness (MDI), is one of the most common, severe, and persistent mental illnesses. Bipolar disorder is a serious lifelong struggle and challenge [2,3,4].

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 psychotropics (e.g., antidepressants, antipsychotics, benzodiazepines) for optimal stabilization.

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 [5].

Levetiracetam is a novel anticonvulsant that is currently investigated in bipolar disorder. It may be useful in the treatment of refractory and complicated cases, in which conventional mood stabilizers are not effective [6]. 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.

### *Aims and objectives*

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.

## MATERIAL AND METHODS

### *Study Area & 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.

***Corresponding Author:**
**Dr. K. K. Daryani,**
Associate Professor,
Department of Pharmacology,
NSCB Medical College,
Jabalpur, India.

***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 (7) 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 (8) 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 lithum therapy and were supposed to receive Lamotrigine, were started with 50 mg/d and the dose was escalated to a maximum of 300mg/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 25mg/d and the dose was escalated to a maximum of 200mg/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.

***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.
- Remission criteria included a 17 items of the Hamilton depression scale below 7.

***First 17 items of the Hamilton depression scale (7)***

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

**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 |

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.

***Efficacy of lamotrigine group***

**Table 2:** Mean Ham-D Scores

| DAYS | HAM – D SCORE (mean ± S.D) |
|---|---|
| DAY 0 | 21.07±2.96 |
| DAY 15 | 18.27±2.88 |
| DAY 30 | 14.85±2.77 |
| DAY 45 | 12.38±3.24 |
| DAY 60 | 10.35±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 |
| ≤50% | 10 |

Total 61.5% patients had shown marked improvement HAM-D at day 60.

***Efficacy of levetiracetam group***

**Table 4:** Mean Ham-D Score

| DAYS | HAM – D SCORE (mean ± S.D) |
|---|---|
| DAY 0 | 21.30±3.80 |
| DAY 15 | 18.86±3.67 |
| DAY 30 | 17.07±4.21 |
| DAY 45 | 15.78±4.46 |
| DAY 60 | 13.81±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 5:** Change in Ham-D Score

| REDUCTION IN HAM-D SCORE | NO. OF PATIENTS (n=27) |
|---|---|
| >50% | 9 |
| ≤50% | 18 |

Total 61.5% patients had shown marked improvement HAM-D at day 60.

**Table 6:** Comparison of Lamotrigine and Levetiracetam on Ham-D Scale

| | LAMOTRIGINE (n=26) | | LEVETIRACETAM (n=27) | |
|---|---|---|---|---|
| | REDUCTION IN HAM-D | | REDUCTION IN HAM-D | |
| | >50% | ≤50% | >50% | ≤50% |
| NO. OF PATIENTS | 16 | 10 | 9 | 18 |

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

## 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 comparison between these two drugs on the basis of HAM-D 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.*, [9] 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 colleagues [10] found that Lamotrigine was superior to placebo in treating major depressive episodes (Lamotrigine 100 mg/day: 85% vs placebo: 30%; *P*<0.05).

The efficacy of Levetiracetam was comparable to the study done by Stephanie Krüger, an open-label trial on 34 patients with treatment-refractory bipolar I disorder received 500-1000mg of Levetiracetam titrated, A 31% remission rate was reported in patients who were depressed at baseline and who received Levetiracetam as an add-on therapy [94].

## 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 more efficacious than Levetiracetam in reducing depressive symptoms in patients presenting with depressive phases of bipolar I and bipolar II disorder.

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