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Research Article

Evaluation of Lamotrigine in Bipolar Depression: Focus on Psychosocial Factors Affecting Response to Treatment and Patient Satisfaction with Medication

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Abstract

TIntroduction: Bipolar disorder is a difficult to treat condition where mood stabilizers play a major role along with adjunctive therapy.

Objectives: Objectives of this study were to evaluate Lamotrigine in the treatment of Bipolar depression; to assess the role of psychosocial factors in modifying the response to treatment and also to evaluate treatment satisfaction with medication.

Methodology: Patients diagnosed with bipolar disorder receiving Lamotrigine with or without other mood stabilizers were administered Hamilton rating scale for depression (HAM-D) at week 0 and week 4. The HAM-D scores were compared to evaluate efficacy. Patients were also administered a Trauma Experience Checklist (TEC) at week 0 to report whether any traumatizing event existed in their life that could modify response to treatment. These events were classified as acute, chronic or no stressor. HAM-D scores in patients with different stressors were evaluated to find out if any correlation existed between stressors and response to treatment. A questionnaire regarding patient satisfaction with treatment (TSQM version 1.4) was administered at week 4. Mann-Whitney U test and Wilcoxon Rank Sum tests were used for calculating the statistics and p value <0.05 was considered significant.

Result: 37 patients diagnosed with bipolar disorder receiving Lamotrigine 200mg/day were enrolled in the study. 13 patients received other mood stabilizers like lithium or valproate. Adjunctive drugs included hypnotics, antipsychotics, antidepressants and miscellaneous drugs. There was significant improvement in HAM-D scores in patients with mild, moderate and severe depression. There was significant improvement in depression associated parameters like depressed mood, suicidal thoughts, anxiety, insomnia, somatic symptoms and work and activities. Patients with no stressors and acute stressors showed a greater response to therapy as compared to chronic stressors. In them the response was significant. Patient satisfaction with treatment was 93% both in euthymic patients and patients with depression.

Conclusion: lamotrigine is efficacious in the treatment of Bipolar disorder; both for maintenance of euthymia and improvement of depression. Presence of chronic stressors in patient's life have a detrimental effect on response to treatment as compared to no stressors and acute stressors. We found patient satisfaction with treatment of about 93%.

Keywords: *Lamotrigine; Bipolar Depression; Patient Satisfaction With Treatment; Trauma Experience*

Introduction

Bipolar disorder is associated with changes in a person's mood, energy and ability to function. The depressive phase of bipolar disorder termed as bipolar depression is associated with depressed mood most of the day with suicidal thoughts, fatigue, loss of interest and insomnia [1]. Bipolar disorder is a leading cause of medical disability worldwide and despite the advances in medical technology, it can only be managed, not cured.[1] The patient has frequent relapses to either mania or depression thereby affecting the quality of life.

Use of various treatment options is guided by the phase of illness (mania/hypomania/depression/mixed) with which the patient presents and past treatment history [2]. The goal of management is to achieve euthymia, normal level of functioning and to avoid switching to hypomanic/manic episode or a depressive episode. The drugs used for maintenance should keep the mood stable without tipping the scale to either pole of the disease. The treatment of depression should alleviate the negative symptoms, but not to the extent where the positive symptoms of mania are triggered.

Treatment options for management of bipolar depression (BPD) can be broadly classified as mood stabilizers, antidepressants, antipsychotic medications, electroconvulsive therapy (ECT), adjunctive medications and psychosocial interventions. The mainstay of management of bipolar depression is mood stabilizers. The available mood stabilizers include Lithium, Valproate, Lamotrigine, Carbamazepine, Oxcarbazepine and Topiramate [3].

Lamotrigine an antiepileptic is FDA approved (2003) for maintenance therapy in bipolar disorder. Mechanism for its antiepileptic action includes inhibition of the voltage-sensitive sodium channels of the neuronal membrane, inhibition of the release of the excitatory amino acids such as glutamate and aspartate and blockade of the calcium-channels [4]. The probable mechanism responsible for Lamotrigine's mood stabilizing action is a positive effect on the corticolimbic network function, which is abnormal in bipolar depression [5]. Little research has been done on lamotrigine in our country, so we decided to evaluate the efficacy of Lamotrigine in patients with bipolar disorder.

Patient satisfaction with treatment affects compliance with medication and compliance affects efficacy. Medication of Bipolar disorder needs to be taken long term, so we decided to evaluate patient satisfaction with Lamotrigine treatment.

The etiology of bipolar disorder is not well understood. Genetics, life events, traumas and certain stressors may play a role in the course of the disorder and the response to treatment [6]. The response to treatment does not depend on medication alone; psychosocial factors like the family life of the patient, and life stressors should not be undermined [7]. Hence we evaluated the psychosocial factors in the response to treatment with Lamotrigine.

Aims And Objectives

To evaluate the efficacy of lamotrigine in patients with Bipolar depression along with the psychosocial factors that could modify the response to treatment. The patient satisfaction to medication was also evaluated.

Methodology

Study design

This study was conducted at the Department of Psychiatry in a tertiary care teaching hospital, after the approval of Institutional Ethics Committee (IEC). This was a prospective, observational, follow up study conducted in a span of 2 months. Patients who attended Out Patient Department (OPD) of Psychiatry department, diagnosed with Bipolar Disorder and receiving Lamotrigine for treatment were included in this study. The sample size was duration based.

All confirmed cases of bipolar disorder as diagnosed by the treating physician conforming to the inclusion criteria were included in the study. Data regarding age, gender, duration of disease, co-existing medical condition, family history and concurrent drugs prescribed was collected using a case record form. Confidentiality of the data was maintained. The patients were subjected to three scales; Hamilton Rating Scale for Depression, Trauma experience check list and Patient satisfaction with treatment questionnaire.

Inclusion criteria

- Patients 18 years and above and either gender.
- Patients able to give written informed consent.
- Confirmed cases of bipolar disorder i.e. those with a history of a manic or hypomanic episode in the past.
- Patient on Lamotrigine for at least a month with or without any other mood stabilizer.

Exclusion criteria

- Patient with coexisting severe medical illness.
- Patients having lack of comprehension.

Questionnaires

Hamilton rating scale for depression

The Hamilton Rating Scale for Depression (HRSD), also known as the Hamilton Depression Rating Scale (HDRS) or abbreviated to HAM-D, is a multiple-choice questionnaire that clinicians may use to rate the severity of a patient's depression [8]. The clinician selects a response to each question by interviewing the patient and by observing the patient's symptoms. There are 17 questions, each addressing a particular symptom of depression and the answer to each range from 0 to 2 or 4, depending on the question. 0 indicates absence of the symptom whereas a full score indicates maximal presence of the symptom. The scores are analyzed as follows; Score 0 to7 is Normal; 8 - 13 is mild depression; 14-18 is moderate depression, 19 - 22 is severe depression; 23 and more is very severe depression.

Trauma experience checklist

The trauma experience checklist (TEC) [9] is a report addressing potentially traumatizing events or stressors. Preliminary findings suggest that the TEC is a reliable and valid self-report instrument that can be used in clinical practice and research. Based on this scale, the stressors were divided into acute and chronic stressors. Acute stressors included events or conditions which were present at the beginning of the disease, but were not present in the course of the disease. They are short term stressors which include death of a close family member i.e. parents, spouse, children; loss of job etc. Chronic stressors included stressors which were present at both, the beginning of the disease and during its course. They include family problems i.e. history of abuse, hostile environment, persisting fear etc.

Treatment satisfaction questionnaire for medication

The Treatment Satisfaction Questionnaire for Medication (TSQM) Version 1.4 is a reliable and valid instrument to assess patients' satisfaction with medication in chronic diseases, providing scores on four scales - side effects, effectiveness, convenience and global satisfaction [10]. Satisfaction with treatment is directly proportional to adherence. There are 14 questions. The lowest score for each item

is 0 indicating dissatisfaction and the highest score is variable, from 5 to 8. The total possible score is 80, with higher scores indicating greater satisfaction with medication.

Study timeline review

At the point of first contact taken as day 1 or week 0, informed consent form, HAM- D scale, TEC scale was filled. After 4 weeks HAM-D scale and TSQM version 1.4 was filled. The HAM-D scores at week 0 or time of first contact were compared with scores at the end of 4 weeks to evaluate efficacy.

Statistical analysis

Data was entered into Microsoft Excel 2016 version. The data was analyzed for effectiveness and other different variables. All the statistical analysis was done using SPSS (Statistical Package for Sciences) version 23.0 (IBM corporation California). The data was not normal in distribution. Mann-Whitney U test and Wilcoxon Rank Sum tests were used for calculating the statistics and p value < 0.05 was considered significant.

Observations And Results

A total of 37 patients suffering from bipolar disorder who were undergoing treatment with Lamotrigine 200mg/day with or without other mood stabilizers were selected from the out-patient department of psychiatry of a tertiary care hospital in this study.

Demographic characteristics

The mean age of patients was estimated to be 42.5 ± 10.15 years. There was a slight preponderance of males compared to females in the study with 20 males and 17 females. The mean duration of Bipolar disorder was 6.89 ± 6.57years. Four patients out of 37 (10.81%) had a first-degree relative suffering from bipolar disorder.

Administration of concurrent drugs

Lamotrigine was not given as monotherapy. 24 patients received Lamotrigine as the only mood stabilizer. 11 patients received dual mood stabilizer therapy; Lamotrigine plus Lithium in 3 patients; Lamotrigine plus Sodium valproate in 7 patients and Lamotrigine plus Oxcarbazepine in 1 patient. 2 patients received three mood stabilizers i.e. Lamotrigine, Lithium and Valproate figure 1.

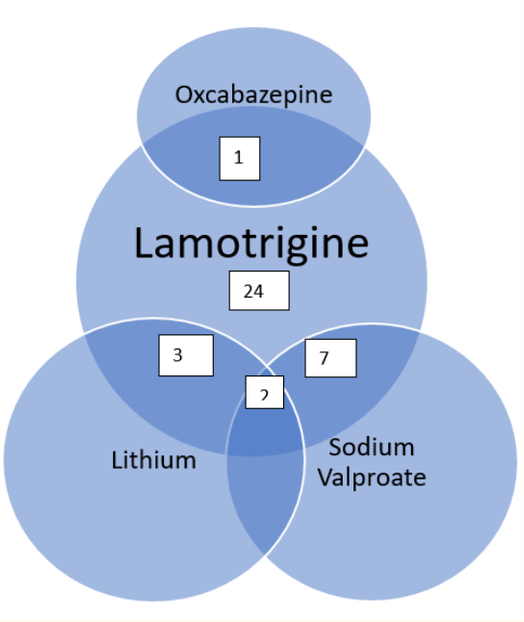

Figure 1: *Frequency Distribution of Mood Stabilizers. Figures indicate the number of patients receiving Mood Stabilizers.*

Adjuvant therapy included hypnotics; Lorazepam in 13 and Clonazepam in 4 patients. Antipsychotics prescribed were Olanzapine (5 patients), and Quetiapine (3 patients). Antidepressants (8 patients) prescribed were Fluoxetine, Sertraline and Amitriptyline table 1. Miscellaneous drugs included multivitamins, Calcium, proton pump inhibitors and folic acid.

Drug class	Number of patients
Hypnotics	17
Antidepressants	8
Antipsychotics	8

Table 1*: Frequency Distribution of Concurrent Medications.*

On an average, 2.64 **±**1.53 (Mean ± SD) drugs were prescribed per patient.

Distribution of depression severity

The Hamilton Depression Rating Score (HAM-D score) taken on the first visit of the patient are mentioned as 'Pre'. The scores obtained on follow up after 4 weeks are mentioned as 'Post'. Based on the pre-scores, the patients were categorized into normal or euthymic (14 patients); these patients formed Group 1. 23 patients had varying severity of depression. Mild depression (8 patients), moderate depression (10 patients) and severe depression (5 patients). These patients formed Group 2. Post scores obtained for both groups were compared with Pre-scores and percentage improvement was calculated as shown in table 1. It was also observed that the average number of drugs prescribed increased as a direct function of severity of depression. (Table 2) Group I patients who were euthymic at the beginning of the study received an average number of 1.7±0.8 number of drugs where as those with severe depression received an average of 3.9±1.6 drugs.

Groups		Number Of Patients	Number Of Drugs Prescribed Mean ± SD	Preham-D Scores Mean ± SD	Post HAM-D Scores Mean ± SD	Percentage Improvement
Group 1		14	1.7 ± 0.8	3.42 ± 3.41	2.99 ± 3.39	12.57% (euthymic state maintained)
Group 2	Overall	23	3.17 ± 1.64	15.261 ± 4.2	3.696 ± 4.4	75.78% *
	Mild depression	8	2 ± 1.4	11.875 ± 1.25	4.75 ± 3.536	60% **
	Moderate depression	10	3.6 ± 0.89	15.7 ± 1.636	3.4 ± 3.062	78.3% *
	Severe depression	5	3.9 ± 1.6	21 ± 2.121	4.8 ± 8.485	77.14% *

Table 2: *Efficacy of Lamotrigine in Both Treatment Groups.*
*Statistically Significance: *P<0.01, **P<0.05.*

Significant improvement in HAM-D scores as seen in the following individual parameters: Depressed mood, suicidal thoughts, insomnia, anxiety, work and activities and somatic symptoms table 3.

Hamilton Depression Scale Parameter	Score Range	Pre-Score Mean ± SD	Post Score Mean ± SD	% Improvement
1. Depressed Mood	0-4	2.522 ± 1.03	0.870 ± 0.967	65.5% *
2.Guilt feeling	0-4	0.522 ± 0.8458	0.217 ± 0.51	58.33%
3.Suicide thoughts	0-4	1.174 ± 1.64	0 ± 0	100%*
4.Insomnia – early	0-2	1.696 ± 0.7029	0.217 ± 0.5997	87.17%*
5.Insomnia – middle	0-2	1.174 ± 0.9367	0.130 ± 0.4577	88.88%*
6.Insomnia – late	0-2	1.087 ± 0.9493	0.043 ± 02085	96%*
7.Work and activities	0-4	1.783 ± 1.04	0.391 ± 0.7223	78.04%*
8.Retardation	0-4	0.130 ± 0.4577	0.087 ± 0.4170	33.33%
9.Agitation	0-2	0 ± 0	0 ± 0	-
10.Anxiety - psychic	0-4	2.522 ± 1.3	0.783 ± 1.12	68.96%*
11.Anxiety - somatic	0-4	1.261 ± 1.28	0.478 ± 1.08	62.06%*
12.Somatic symptoms – GI	0-2	0.522 ± 0.79	0.087 ± 0.2881	83.33%*
13.Somaticsymptoms-general	0-2	0.652 ± 0.6473	0.261 ± 0.4490	60%*
14.Genital symptoms	0-2	0.043 ± 0.2085	0 ± 0	100%*
15.Hypochondriasis	0-4	0.214 ± 0.5789	0.043 ± 0.2085	66.66%*
16.Loss of weight	0-2	0.043 ± 0.2085	0.087 ± 0.2881	10.23%
17.Insight	0-2	0 ± 0	0 ± 0	-
Total score	0-50	15.261 ± 4.19	3.696 ± 4.38	75.78%*

Table 3: *Pre and post scores of Ham-D scales in GROUP 2 patients (n=23).*

** Statistically significant.*

Stressors in bipolar depression (Trauma experience)

Out of 37 patients, 33 patients consented for the administration of TEC. On administration of this questionnaire, it was found that 25 (75.7%) patients had 1 major life stressor. No patient had more than 1 type of stressor. 8 patients had no identifiable stressors.

The patients were broadly divided into those with acute stressors, chronic stressors or no stressor. The acute stressors included death of a loved one, loss of job etc. The chronic stressors included persisting family problems (parental abuse, abuse by spouse, hostile environment at home), fear etc.

10 patients gave history of acute stressors. Death of loved one in case of 9 patients, loss of job in 1 patient. 15 patients had chronic stressors; family problems were present in 10 and history of fear was seen in 5. Cause of fear was unknown in 2 patients. 8 patients had no identifiable stressors.

Comparison of Hamilton depression scores in patients with acute, chronic and no stressors

The patients were divided in these 3 categories of acute, chronic and no stressors and their HAM-D scores were analyzed to see if there was any correlation between the stressors and response to treatment. The response to treatment was maximum in case of patients with

no stressor, followed by patients with acute stressors and chronic stressors respectively. The response to treatment was statistically significant in case of patients with no stressor and acute stressors. These results are graphically represented in figure 2.

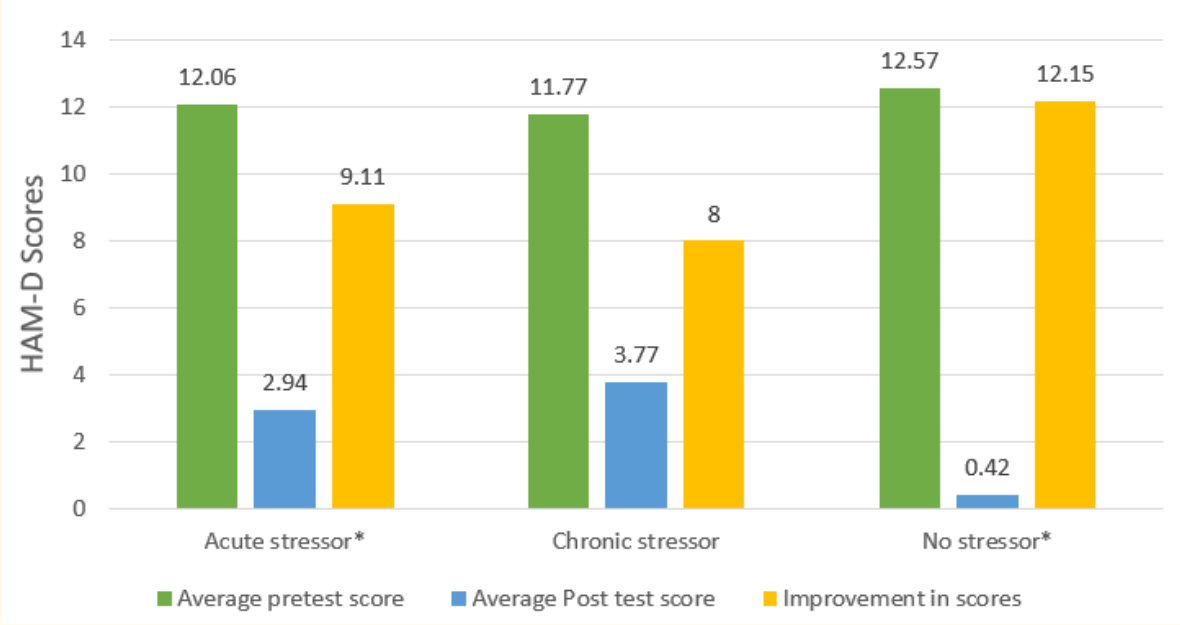

Figure 2: *Effect of Stressors on Response to Treatment.*

** Statistically significant, P<0.05.*

Satisfaction with treatment

The different aspects of satisfaction to treatment was demonstrated using the treatment satisfaction questionnaire (TSQM) for medication. It shows that 93.47% of patients in GROUP 1 (patients with euthymia at the beginning of the study) are satisfied with treatment. 93.07% of patients in GROUP 2 (patients with varying degrees of depression at the beginning of the study) are satisfied with treatment. The difference between the two treatment groups was not statistically significant.

Discussion

We found very few studies on Lamotrigine as a mood stabilizer in India. This prompted us to take up this study. Management of Bipolar illness usually requires long term therapy. The management of depressive phase is more arduous as compared to the maniac phase with frequent relapses which makes the treatment unsatisfactory [1]. Conventional anti-depressants cannot be used in bipolar depression since they cause a switch to mania. Hence, the appropriate drug for bipolar depression needs to alleviate the symptoms of depression without causing the tip over to the manic phase [2].

This prospective, observational follow up study was carried out at the Department of Psychiatry of a tertiary care teaching hospital. A total of 37 patients visiting the outpatient department of Psychiatry diagnosed with Bipolar disorder and taking lamotrigine were included in the study, after taking their informed consent. This study was carried out in a span of two months.

This study analyzed the efficacy of Lamotrigine in Bipolar depression using the Hamilton D scale for Depression. We also evaluated patient satisfaction to treatment using Treatment satisfaction to medication (TSQM) questionnaire. The psychosocial factors affecting response to treatment were analyzed using Trauma experience checklist (TEC).

These 37 patients of Bipolar disorder received Lamotrigine 200 mg/day with or without other mood stabilizers. There was a slight preponderance of males as compared to females in our study. Although gender differences in distribution of bipolar disorder have not been noted as are seen in unipolar depression [11]. The mean age group of presenting patients was 42.5 ± 10.15 years. Majority of patients were between 41 - 50 years of age. Mean duration of illness was 6.89 years. The average number of drugs the patients received were 2.64 ± 1.53 drugs.

Efficacy of lamotrigine

There was improvement in depression in both groups of patients i.e. Group 1 where the pre-scores implied normal mood or euthymia as well as Group 2 where the pre-scores showed varying degrees of depression. The improvement was statistically significant in Group 2 patients. This implies that Lamotrigine maintains euthymia in patients whose HAM-D scores were in the normal range but significantly improves mood in depressed patients. Results show that among the different parameters of HAM-D scale significant improvements were seen in depressed mood, suicidal thoughts, insomnia, anxiety, work and activities. A multicentric study on treatment of bipolar disorder with Lamotrigine as add on treatment with special attention on rate of relapse, suicidal behavior and adverse events showed that suicide rate decreased from 17 to 2.1%. No suicide attempt or completed suicide occurred during the study period [12]. This study showed that lamotrigine was effective and well tolerated for both acute as well as long term treatment of Bipolar disorder.

In another study by Goodwin GM., *et al.* Lamotrigine was compared to Lithium as a mood stabilizer. Both Lamotrigine and Lithium were superior to placebo for the prevention of relapse or recurrence of mood episodes in patients with bipolar I disorder. The results indicated that Lamotrigine was an effective, well-tolerated maintenance treatment for bipolar disorder, particularly for prophylaxis of depression. It was observed that Lamotrigine prolonged the relapse to depression while Lithium had a greater efficacy in prolonging the relapse to mania [13].

In our study 11 patients received dual mood stabilizer therapy and 2 received triple mood stabilizer therapy; so, in these patients' improvement in depression cannot be solely attributed to lamotrigine alone. Recent reviews have highlighted a greater role of Lamotrigine in bipolar depression as compared to mania. Lamotrigine causes stabilization from "below baseline" in contrast to Lithium which causes stabilization from "above baseline [14]. Lamotrigine has been called a depression mood stabilizer.

A randomized placebo-controlled 7-week study compared two doses of Lamotrigine; 50 mg/day and 200 mg/day with placebo in 195 patients with moderate to severe bipolar depression. Lamotrigine was superior to placebo after 3 weeks. There was no evidence that Lamotrigine destabilized mood or precipitated mania. Tolerability was good and there were no cases of serious rashes [15]. In our study patients received 200mg of Lamotrigine/day; however, we did not differentiate between bipolar 1 and bipolar 2 patients as our sample size was very small. A meta-analysis of studies done on Lamotrigine concluded that Lamotrigine is efficacious for maintenance of Bipolar disorder when depression is a prominent feature [5].

Psychosocial factors and response to treatment

The exact cause of bipolar disorder is unknown. But a widely accepted hypothesis is the diathesis stress model, which states that there are certain stressors (life events, death of a loved one, family problems etc.) which increase the risk of bipolar disorder [16]. And since psychosocial factors include parameters that can significantly modify the response to treatment, they need to be studied in detail. However, very few studies identifying these stressors for bipolar disorder have been done in India.

In this study, it was observed that acute stressors were death of a loved ones and loss of job; and the chronic stressors were family problems and persisting fear. The response to treatment was significant in patients with no stressors (96.65%), followed by patients with acute stressors (75.6%). It was not significant in patients with chronic stressors (67.8%).

This indicates that the constant presence of the stressor may have a negative influence on response to treatment. So, patients with chronic stressors may require a greater focus on psychotherapy. This result highlights that a healthy, supportive environment has a positive impact on response to treatment. A prospective, longitudinal study done on 131 patients of bipolar disorder in USA in 2013 showed that interpersonal stressors were predictive of depressive symptoms [17].

A prospective longitudinal study was done in USA with 23 relatives of patients with Bipolar disorder. This study evaluated the attitude of relatives towards the patient. It was observed that the chances of mood destabilization were increased in case of hostile atmosphere at home [18]. Results suggest that the emotional atmosphere of the family may be an important predictor of the clinical course of bipolar disorder.

Treatment satisfaction with lamotrigine

A drug has little value if the patients do not comply to therapy, especially in a chronic disease like bipolar disorder where the patients need to be on medication for most of their lives. Patients will only comply with the therapy if they feel that medication is producing benefit without producing intolerable adverse effects. Hence, patient satisfaction with Lamotrigine is a very important parameter to consider. In this study treatment satisfaction in both groups of patients was similar; 93.07% patients in Group 1 and 93.07% patients in Group 2 exhibited satisfaction with treatment. The difference between the groups was not significant.

This study is first of its kind observational follow up study done in our setup where Lamotrigine was evaluated in bipolar depression. The other positive aspects of this study are use of two novel tools; TEC for studying the effect of stressors on response to treatment and TSQM for evaluating patient satisfaction with Lamotrigine treatment. In fact, treatment satisfaction with lamotrigine has not been documented in literature before this though it has been done for Teriflunomide in a disease like Multiple Sclerosis [10]. Application of these tools help the researchers to identify stressors which could contribute to illness. Evaluation of treatment satisfaction will go a long way in identifying patient adherence to treatment; which would eventually transform into successful therapy. Our study has certain limitations in the form of less duration and limited sample size. Hence efficacy parameters could not be measured beyond 4 weeks. So, the role of Lamotrigine for long term prophylaxis could not be established with certainty. As some patients received more than one mood stabilizer the results cannot solely be attributed to Lamotrigine in these patients. In future, if a larger sample size is available, authors would like to study the role of lamotrigine in bipolar 1 disorder as Lamotrigine which stabilizes the mood from below baseline has a greater efficacy in Bipolar 1 as compared to Bipolar 2 disorder [5].

Conclusion

To conclude, Lamotrigine is efficacious in the prophylaxis and treatment of Bipolar depression. It has modest efficacy in mild depression, but greater efficacy in moderate and severe depression. Lamotrigine improves associated symptoms of depression like anxiety, suicidal thoughts and disinterest in work and activities. This study shows that response to treatment is affected by life stressors. Patients with no stressors and acute stressors respond better as compared to patients with chronic stressors. Satisfaction with treatment is in the range of 90% based on TSQM questionnaire.

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