Original Research Article

Effectiveness of mood stabilizer in euthymic BPAD patients: An one year prospective observational study, comparing Lithium v/s Divalproate sodium

Suresh Kumar Ramasamy[1], Syed Ummar Ibrahim[2], Sarah Afreen[3], Sendhil Raj[4]

[1]Assistant Professor, [2]Associate Professor, Department of Psychiatry, PSG Institute of Medical Science and Research, Coimbatore, INDIA.
Email: side_ummar@yahoo.com

Abstract

Background: Bipolar disorder is potentially a lifelong and disabling condition, which requires long-term pharmacological therapy as maintenance treatment. Lithium is considered as first-line mood stabilizer, followed by Divalproate, both are known to reduce the risk of relapse. However, relapses do occur and these medications are also associated with side effects. We aimed to compare the mood stabilizing effect between Lithium and Divalproate in our prospective study. **Methods:** 104 bipolar patients who were euthymic (52 patients each on Lithium and Divalproate therapy) were followed up for one year with periodic evaluation done during initial, 3rd, 6th, 9th and 12th month. Time taken to relapse, severity of mood episode, suicidal risk and functioning were assessed using standardized scales. Compliance to medications and adverse effects were also assessed. **Results:** The duration of treatment was for a longer period in Lithium group (p=0.001) and this was the only confounding variable which was significant. Patients who are taking Divalproate had more severe manic episode at the end of 1 year when compared to patients taking Lithium (p=0.041). Patients on Lithium also had lesser suicidal risk (trending towards significance). **Conclusions:** There was no difference in terms of frequency of depressive episode, adherence, adverse effects and global functioning between the two groups. But Lithium group patients had less frequent and less severe manic episodes and lower suicidal risk, favoring Lithium to be a better mood stabilizer, with less adverse effects and better quality of life.
Key Word: Bipolar disorder; Mood stabilizer; Maintenance treatment; Quality of life.

***Address for Correspondence:**
Dr. Syed Ummar Ibrahim, Associate Professor, Department of Psychiatry, PSG Institute of Medical Science and Research, P.O. Box No: 1664, Avinashi Road, Peelamedu, Coimbatore - 641 004, Tamil Nadu, INDIA.
Email: side_ummar@yahoo.com
Received Date: 30/03/2019 Revised Date: 23/04/2019 Accepted Date: 11/06/2019
DOI: https://doi.org/10.26611/1071033

Access this article online	
Quick Response Code:	Website: www.medpulse.in
	Accessed Date: 24 June 2019

INTRODUCTION

Bipolar Affective Disorder (BPAD) is one of the most disabling mental illnesses affecting most productive period of life at the age 15-45years.[1] Lithium carbonate has been a gold standard treatment for past five decades. But it has a narrow therapeutic index and significant adverse effects.[2] Anticonvulsants such as Divalproate sodium, Carbamazepine and Oxcarbamazepine, have been proposed as an alternative, also have more adverse effect profile and their comparative efficacy with Lithium is uncertain.[3-8] Lithium Carbonate as a mood stabilizer has been a superior agent to reduce the risk of relapse and to prevent suicidal behaviours.[2-7] In view of its adverse effects, tolerance becomes an issue; which can interfere with adherence.[4-7] Lithium causes multiple skin reactions, the most common are acne and psoriasis. The prevalence of skin reaction with Lithium ranges between 3-34 %. Some studies have shown high chance of discontinuation of Lithium is due to adverse skin reactions.[9] Anticonvulsants approved by FDA, has the next level of

How to cite this article: Suresh Kumar Ramasamy, Syed Ummar Ibrahim, Sarah Afreen, Sendhil Raj. Effectiveness of mood stabilizer in euthymic BPAD patients: An one year prospective observational study, comparing Lithium v/s Divalproate sodium. *MedPulse – International Journal of Psychology*. June 2019; 10(3): 27-34. http://www.medpulse.in

evidence as a mood stabilizer but their long term safety and efficacy in comparison with Lithium remains uncertain[7] Randomised controlled trails have shown superiority of Divalproate sodium to placebo.[10-11] Divalproate sodium has been comparable with Lithium in Manic episode[11] FDA approved mood stabilisers for the treatment of bipolar affective disorder are Lithium, Divalproate sodium, Carbamazepine and Lamotrigine.[17-20] Mood stabilisers can also be used as monotherapy which was approved by FDA.[21-22] Mania with two or more episodes of depression showed a good improvement with Divalproate sodium than Lithium.[23-24] Lithium and Divalproate sodium showed more effect than any other mood stabilisers during acute phase of mania and in maintenance phase.[25-27] Olanzapine, Risperidone and Quetiapine are FDA approved atypical antipsychotics for the acute phase of mania[17,18,20] According to BALANCE study both Lithium monotherapy and combination therapy with Lithium and Divalproate sodium are more likely to prevent relapse than Divalproate sodium monotherapy, irrespective of baseline severity of illness and is maintained for up to 2 years.[12] Bowden *et al*, in his randomized placebo controlled 12 months trial of Lithium v/s Divalproate sodium, has shown no significant difference between the two groups in terms of time to recurrence of mood episode during maintenance therapy. Compared to placebo, Divalproate sodium has lesser discontinuation rate[13.] Even though open labelled trails favours Divalproate sodium in reducing the frequency and intensity of further episodes, there are less comparative study with Lithium in maintenance therapy.[14-16] Long term outcomes are often poor in patients with bipolar disorder despite treatment; therefore more effective treatments are needed to reduce recurrences and morbidity. Hence, we proposed a prospective comparison study of Lithium and Divalproate sodium in euthymic BPAD patients for a period of at least 1year during the maintenance phase. We aimed to compare the mood stabilizing properties of Lithium and Divalproate sodium in BPAD patients. Our other objectives are to evaluate the time taken for relapse of any mood episodes (mania/depression/mixed episodes), assess the severity of the mood episodes, episodes of deliberate self harm, adherence to study treatment, adverse effects of medications and global assessment of functioning.

METHODS

Study design: This is a prospective observational study done in patients with bipolar affective disorder who came to the psychiatry department in PSG Institute of Medical Sciences and Research, Coimbatore, India. A total of 104 bipolar affective disorder patients were recruited from out-patient setting. The study protocol was explained to the participants, and a written informed consent was obtained from the patient. If patient could not consent, it was obtained from the family member and later from the patient when he/she could consent. The study was approved by Institutional Human Ethics Committee.

Study participants: Men and women aged 18 years and above who received a clinical diagnosis of BPAD (as per ICD-10 criteria) in psychiatry out-patient department were eligible for the study. Patients were initiated or continued on a single mood stabilizer either on Lithium or Divalproate sodium. Only patients who achieved remission within 2 months of follow-up were included in the study. Patients who were already on more than one mood stabilizers (Lithium, Valproate, Carbamazepine, Lamotrigine, Gabapentin and Topiramate) during index diagnosis and medically unstable patients with conditions such as renal failure, liver cirrhosis, severe diabetes, arrhythmia etc. were excluded from the study.

Assessment: After recruiting the patients as per our inclusion and exclusion criteria, 52 patients who were on Lithium therapy and 52 patients who were on Divalproate therapy, were prospectively followed up for 1 year period. Patients were evaluated by the investigator, following 2 months of euthymic period (index evaluation). During follow up patients were evaluated at 3rd, 6th, 9thand 12th month respectively (periodic evaluation). Patients who are missing on follow up are contacted through telephone and requested to come for follow-up and assessed. As it is an observational study, investigators took no role in modifying the dosage of medications, but it was taken care by the primary incharge treating team. During initial evaluation, a semi-structured proforma (socio-demographic details and other confounding variables) is administered. Diagnosis was confirmed by applying a SCID (Structured Clinical Interview for DSM-IV) version for mood disorder. As per earlier literature available, remission is a state that comes close to being symptom free. By which the euthymic status of the patient was ascertained by applying HAM-D and YMRS rating scales. Typically remission should have a score of ≤ 7 on HAM-D and ≤ 2 on YMRS. Severity of suicidal ideas is assessed by Modified SADPERSONS Scale. Global Assessment of Functioning was assessed using a GAF scale. The dosage of the mood stabilizer could be altered by the primary in-charge team based on serum concentration of the drug/adverse effects, during 1 year maintenance period. Participants who remain on the allotted treatment for 1 year of study were periodically evaluated. Use of other psychotropics was allowed during the study trial (antipsychotics, benzodiazepines).Periodic assessment was done as per the figure 1 given below, for confounding variables, SCID-mood disorder sub-scale,

Young Mania Rating Scale (YMRS)/ Hamilton rating scale for Depression (HAM-D) appropriate to the patient (to access the severity of episode if any), Modified SADPERSONS scale-to see suicidal score, adverse drug reaction and Global assessment of functioning (GAF) scale.

Statistical analyses: Statistical analyses were conducted using software package SPSS version 20. We compared the efficacy of Lithium and Divalproate sodium with the following variables such as age, gender, marital status and education status, which were expressed in percentage and the presence of any statistically significant difference, was analysed using Chi-square test. Also statistically significant difference between the age of onset, number of previous episodes, previous hospitalisation, polarity of previous episodes, psychotropics and duration of mood stabiliser with that of Lithium and Divalproate sodium was done using Chi-square test. Comparison of duration of illness, time taken for any mood episodes, severity of manic episode/depressive episode, suicidal risk, adherence to medications, adverse effects, global assessment functioning between Lithium and Divalproate sodium was done using analysis of variance; p-values <0.05 was considered as significant.

RESULTS

Table 1: Comparison of socio-demographic and confounding variable between Lithium and *Divalproate sodium group*:

Variables		Lithium	Divalproate sodium	p value
Age at recruitment	18- 35 years	31(59.6%)	25(48.1%)	0.392
	36- 59 years	18(34.6%)	21(40.4%)	
	> 60 years	3(5.8%)	6(11.5%)	
Gender	Male	32(61.5%)	39(75.0%)	0.140
	Female	20(38.5%)	13(25.0%)	
Educational status	Illiterate	7(13.5%)	14(26.9%)	0.101
	Up to 10th std	27(51.9%)	20(38.5%)	
	11th-12th	5(9.6%)	10(19.2%)	
	Graduate	13(25.0%)	8(15.4%)	
Marital status	Unmarried	15(28.8%)	11(21.2%)	0.169
	Married, living together	32(61.5%)	26(50.0%)	
	Married, living separately	3(5.8%)	7(13.5%)	
	Married, divorced	1(1.9%)	4(7.7%)	
	Widow/widower	1(1.9%)	4(7.7%)	
Age of onset	< 35 years	19(36.5%)	9(17.3%)	0.085
	36- 59 years	27(51.9%)	36(69.2%)	
	> 60 years	6(11.5%)	7(13.5%)	
Number of episodes	1episode	0(0.0%)	3(5.8%)	0.145
	2episode	18(34.6%)	13(25.0%)	
	>=3episodes	34(65.4%)	36(69.2%)	
Previous hospitalisations	No hospitalisation	7(13.5%)	6(11.5%)	0.594
	1 hospitalisation	9(17.3%)	5(9.6%)	
	2 hospitalisations	15(28.8%)	19(36.5%)	
	>=3hospitalisations	20(38.5%)	22(42.3%)	
Polarity of previous episodes	1 Depressive episode	1(1.9%)	0(0.0%)	0.373
	1 Manic episode	4(7.7%)	6(11.5%)	
	Depression = Mania	18(34.6%)	14(26.9%)	
	Depression > Mania	11(21.2%)	7(13.5%)	
	Mania > Depression	12(23.1%)	12(23.1%)	
	>=2 mania episodes	6(11.5%)	13(25.0%)	
Psychotropics	No drugs	23(44.5%)	13(25.0%)	0.982
	Typical antipsychotics	7(13.5%)	15(28.8%)	
	Atypical antipsychotics	19(36.5%)	21(40.4%)	
	Antidepressants	2(3.8%)	2(3.8%)	
	Benzodiazepines	1(1.9%)	1(1.9%)	
Duration of Mood Stabilizer	<6months	1(1.9%)	0(.0%)	**0.001**
	6months-1year	7(13.5%)	1(1.9%)	
	1- 2years	5(9.6%)	20(38.5%)	
	>2years	39(75.0%)	31(59.6%)	

There was no significant difference between the two groups in socio-demographic variables (Table 1) such as age (p=0.392), gender (p=0.14), educational qualification (p=0.10) and marital status (p=0.17).There is no statistical significance among the confounding variables such as; age of onset (p=0.085), number of episodes (p=0.145), previous hospitalisations (p=0.594), polarity of episodes (p=0.373), psychotropics (p=0.982). Between the two groups, the duration of illness (p=0.001) was the only confounding variable which was significant between the two groups. The number of mood episodes that occurred was; among Lithium group patients 13 had manic episodes and 8 had depressive episodes. Among *Divalproate sodium group* patients 12 had manic episodes and 6 had depressive episodes. In both the groups' manic episodes were more common than depressive episodes.

Time taken for any mood episode relapse to occur: For a manic episode relapse; in the *Lithium group*, 39 patients had no episodes of mania, 5 patients developed mania in less than three months, 4 patients between three to six months and 4 patients between six to nine months. In the *Divalproate sodium group*, 40 patients had no episodes of mania, 2 patients developed mania in less than three months, 3 patients between three to six months, 3 patients between six to nine months and 4 patients between nine to twelve months. The time taken for manic episode was not statistically significant between Lithium and *Divalproate sodium group* (p=0.339). For a depressive episode to occur; in the *Lithium group*, 45 patients had no episodes of depression, 2 patients developed depression between three to six months, 2 patients between six to nine months and 3 patients between nine to twelve months. In the *Divalproate sodium group*, 46 patients had no episodes of depression, 1 patient developed depression in less than three months, 3 patients between three to six months and 2 patients between nine to twelve months. The time taken for depressive episode was also not statistically significant between Lithium and *Divalproate sodium group* (p=0.240).

Severity of mood episodes

Figure 2: Comparison of severity of manic episode between Lithium and *Divalproate sodium group* using YMRS

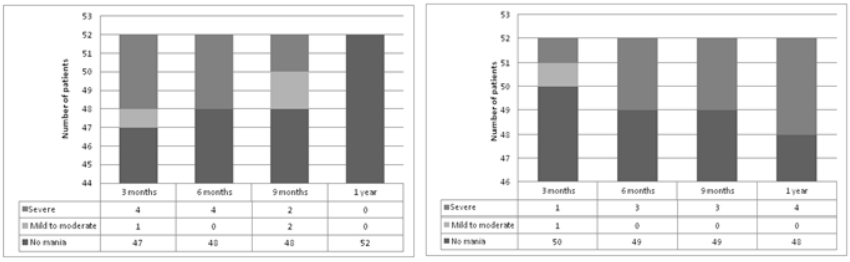

Figure 2A: Figure 2B:

Figure 2 A: Severity of mania in patients taking Lithium; **Figure 2B:** Severity of mania in patients taking Divalproate sodium

The severity of mania was assessed using The Young Mania Rating Scale (YMRS) in Figure2. Patients who are taking Divalproate sodium had more severe manic episode at the end of one year when compared to patients taking Lithium (4 patients v/s none – p=0.041), but the comparison was not significant during initial 3 follow ups at 3, 6 and 9 months (p=0.388, 0.696, 0.331 respectively)

Figure 3: Comparison of severity of depressive episode between Lithium and *Divalproate sodium group* using HDRS:

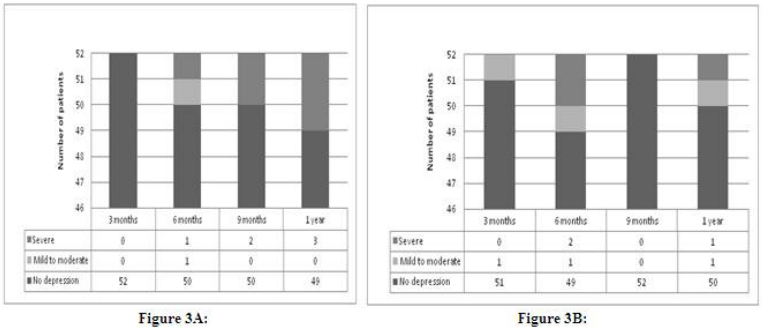

Figure 3A: Figure 3B:

Figure 3A: Severity of depression in patients taking Lithium; **Figure 3B:** Severity of depression in patients taking Divalproate

The severity of depression was assessed using Hamilton Depression Rating Scale (HDRS) in Figure 3. On comparison with patients who are taking Lithium and Divalproate sodium. There was no statistically significant difference in the severity of depressive episode during all four follow ups (3rd, 6th, 9th and 12th month periodic evaluation; p = 0.315, 0.842, 0.153, 0.366 respectively).

Table 2: Suicidal risk assessment between Lithium and *Divalproate sodium group* using Modified SADPERSONS Scale

Groups	No risk	Moderate risk	Severe risk	p Value
		At Baseline		
Lithium	37 (71.2%)	15 (28.8%)	0	
Divalproate sodium	35 (67.3%)	17 (32.7%)	0	0.671
		During *3 months* follow-up		
Lithium	35 (67.3%)	14 (26.9%)	3 (5.8%)	
Divalproate sodium	34 (65.4%)	18 (34.6%)	0	0.173
		During *6 months* follow-up		
Lithium	39(67.3%)	9(26.9%)	4(7.7%)	
Divalproate sodium	34(65.4%)	15(28.8%)	3 (5.8%)	0.371
		During *9 months* follow-up		
Lithium	42(80.8%)	8(15.4%)	2(3.8%)	
Divalproate sodium	40(76.9%)	9(17.3%)	3 (5.8%)	0.857
		During *12 months* follow-up		
Lithium	47(90.4%)	3(5.8%)	2(3.8%)	
Divalproate sodium	38(73.1%)	9(17.3%)	5 (9.6%)	**0.073**

Modified SADPERSONS scale was applied to assess suicidal risk. The severity of suicidal risk scale (Table 2) was not statistically significant during initial and all four follow-ups, but was trending towards significance during the 12th month follow-up (baseline, 3rd, 6th, 9th and 12th month periodic evaluation; p=0.671, 0.173, 0.371, 0.857, **0.073** respectively)**.**

Adherence to study treatment: In the Lithium group of patients; 4 (7.7%) had no follow-up, 5 (9.6%) have followed-up once, 8 (15.4%) have followed-up twice, 10 (9.2%) have followed-up thrice and 25 (48.1%) have been completely followed-up till the end of one year. In the *Divalproate sodium group* of patients; 5 (9.6%) had no follow-up, 4 (7.7%) have followed-up once, 8 (15.4%) have followed-up twice, 13 (25%) have followed-up thrice and 22 (42.3%) have been completely followed-up till the end of one year. Among 104 recruited patients, 25 patients of Lithium group had completed all four follow-ups as compared to 22 patients of *Divalproate sodium group*. But on comparison between the two groups, they were not statistically significant (p=0.938).

Table 3: Adverse effects of the treatment

Groups	No drug reaction	Minimal reaction	More reaction	p value
		At Baseline		
Lithium	28(53.8%)	24(46.2%)	0	
Divalproate sodium	24(46.2%)	26 (50%)	2(3.8%)	0.303
		During *3rd month*follow-up		
Lithium	23(44.2%)	29(55.8%)	0	
Divalproate sodium	24(46.2%)	23(44.2%)	5(9.6%)	0.057
		During*6th month* follow-up		
Lithium	27(51.9%)	25(48.1%)	0	
Divalproate sodium	26 (50%)	24(46.2%)	2(3.8%)	0.361
		During *9th month* follow-up		
Lithium	30(57.7%)	22(42.3%)	0	
Divalproate sodium	35(67.3%)	16(30.8%)	1(1.9%)	0.312
		During *12th month* follow-up		
Lithium	42(80.8%)	10(19.2%)	0	
Divalproate sodium	39(75.0%)	11(21.2%)	2(3.8%)	0.340

The adverse drug effect (categorised as nausea, diarrhoea, tremors, weight gain, sedation, polydipsia, polyuria, tachycardia, alopecia, any major skin lesions, hypothyroid symptoms, signs of renal dysfunction) profile (Table 3) was the same between Lithium and *Divalproate sodium group* during all four visits except during initial follow up (3months) in which Lithium group was better than *Divalproate sodium group* (five patients on *Divalproate sodium group* had >=3 adverse drug reaction compared to none in the Lithium group), which was statistically significant.

Table 4: Global Assessment Functioning

Groups	Good functioning	Mild impairment	Moderate impairment	Severe impairment	p value
		At *Baseline*			
Lithium	51 (98.1%)	1 (1.9%)	0	0	0.315
Divalproate sodium	52 (100%)	0	0	0	
		During *3rd month* follow-up			
Lithium	46(88.5%)	2(3.8%)	3(5.8%)	1(1.9%)	0.553
Divalproate sodium	49(94.2%)	2(3.8%)	1(1.9%)	0	
		During *6th month* follow-up			
Lithium	46(88.5%)	1(1.9%)	3(5.8%)	2(3.8%)	
Divalproate sodium	46(88.5%)	2(3.8%)	2(3.8%)	2(3.8%)	0.912
		During *9th month* follow-up			
Lithium	46(88.5%)	2(3.8%)	3(5.8%)	1(1.9%)	
Divalproate sodium	49(94.2%)	0	1 (1.9%)	2(3.8%)	0.330
		During *12th month* follow-up			
Lithium	49(94.2%)	0	3(5.8%)	0	
Divalproate sodium	46(88.5%)	0	2(3.8%)	4(7.7%)	0.117

On assessment of social, psychological and occupational functioning by using GAF scale (Table 4). During the initial follow ups Lithium group patients had more functional impairment than *Divalproate sodium group* patients (initial and 3rd follow up). During 6th month follow up two patients in each group had severe impairment. During 9th month and 1year follow up, *Divalproate sodium group* had more severe functional impairment than Lithium group, but was not statistically significant.

Comparison of new mood episode with varying serum Lithium level: We also calculated the patients who developed a new manic/depressive episode with varying serum Lithium level. Out of thirteen new episodes manic patients, six had a lower serum Lithium level (<0.8 mEq/L), five patients had serum Lithium level of 0.8-1.2 mEq/L and only two patients had serum Lithium level >1.2mEq/L. Likewise majority of new onset depression episode patient, four out of eight patients had a lower serum Lithium level (<0.8 mEq/L), three patients had serum Lithium level of 0.8-1.2 mEq/L and only one patient had serum Lithium level >1.2mEq/L.

Comparison of new mood episode with varying dosage of Divalproate sodium: Among the *Divalproate sodium group* patients, only three out of twelve patients were on adequate dose (more than 1.5gm), had new onset mania. None of the *Divalproate sodium group* patients had new onset depression that is on adequate dose (all six patients who had new onset depression were on sub-therapeutic dose).

DISCUSSION

In our prospective study of one year duration, we compared the mood stabilising effect of Lithium and Divalproate sodium in euthymic bipolar patients. The socio-demographic and confounding variables did not differ between the two groups except that the Lithium group patients had longer duration of treatment than those treated with Divalproate sodium. As a primary outcome of the study, we compared the frequency of manic and depressive episode between two groups. There were similar number of episodes and the predominant mood episode was mania in both the groups. The above finding could also be because the polarity of previous episode in both the groups was predominantly mania. During the period of 9th to12th month follow up, Divalproate sodium had more manic episodes. The above finding emphasises Lithium to be a better long term mood stabiliser than Divalproate sodium. Previous studies have shown that Lithium treatment reduces the risk of relapse in bipolar disorder. The preventive effect is clear for manic episodes, although it is equivocal for depressive episodes.[5] Lithium appears to be the most effective treatment to prevent recurrence or relapse of bipolar disorder and may prolong the time before adjunctive prescribing is necessary.[28] This finding is further supported by the result of recent meta-analysis[29] suggest that Lithium is superior in prevention of manic episodes, in comparison to anticonvulsants. However, there was no significant difference regarding prevention of overall mood episodes, depressive episodes or study completion. Based on the severity of mood episode; patients on Divalproate arm, had more severe manic episodes as the duration of follow up increased. This again emphasises that Lithium is a better anti-manic agent for long-term therapy. But, the frequency and severity of depressive episodes did not differ between both the groups. On comparison of suicidal risk, bipolar patients who were on Lithium had lower suicidal risk than Divalproate patients, especially with prolonged duration of treatment. Both Lithium and *Divalproate sodium group* patients had almost equal follow ups and were equally adherent to

treatment. Two patients on Lithium were switched to Divalproate sodium as they had severe skin reaction which affected the study adherence. Adverse effect profile did not differ during initial and periodic assessment between the two groups. Bipolar patients on Divalproate sodium had more adverse effects during initial follow ups, which were not seen during further follow up. Global assessment of functioning was done considering psychological, social and occupational functioning on a hypothetical continuum of mental-health illness. Patients on *Divalproate sodium group* had more severe impairment in functioning, than patients in Lithium group. The serum Lithium level was less than adequate in majority of new onset manic/depressive episode patients, signifying that majority of the patients who developed new onset manic/depressive episode were on sub therapeutic dose. Further emphasising the relationship between plasma levels of the drug and relapse prevention.

Limitations: Our sample size was smaller and hence the results cannot be generalised. Telephonic assessments for patients, who missed follow ups, cannot be considered as reliable as face to face interview. Use of other psychotropics (antipsychotics, benzodiazepines) was allowed. We know that medication like Olanzapine, Risperidone and Quetiapine can have a mood stabilising effect, which could have affected the outcome of the study. A follow-up more than 1 year is needed in order to strongly support our finding that, bipolar patients on Lithium were better than Divalproate sodium in preventing the manic episode.

CONCLUSION

Bipolar patients on Lithium had lesser frequent and less severity of manic episode over one year follow up. The frequency of depressive episode was similar between the Lithium and *Divalproate sodium group*s. Lithium exhibited better anti-suicidal properties. Lithium continues to be a gold standard in spite of certain cutaneous side effects establishing its seven decades of dominance as a mood stabilizer agent. In addition, long-term use of Lithium also ensures better quality of life.

Contributors: SU and SA designed this study. SA managed the data collection. SU, SA and KSR analysed the data. KSR wrote the draft of the manuscript under the supervision of SU and SA. All authors contributed to and have approved the final manuscript.

Role of funding source: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

REFERENCES

1. Murray CJL, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. *Lancet* 1997; 349: 1436–42.
2. American Psychiatric Association. Practice guideline for the treatment of patients with bipolar disorder (revision).*Am J Psychiatry* 2002; 159 (4 suppl): 1–50.
3. Goodwin GM. Evidence-based guidelines for treating bipolar disorder: revised second edition—recommendations from the British Association for Psychopharmacology. *J Psychopharmacol*2009; 23: 346–88.
4. National Institute for Health and Clinical Excellence. Bipolar disorder: the management of bipolar disorder in adults, children and adolescents, in primary and secondary care. http://guidance.nice.org.uk/CG38 (accessed Nov 19, 2009).
5. Geddes JR, Burgess S, *et al.* Long-term lithium therapy for bipolar disorder: systematic review and meta-analysis of randomized controlled trials. *Am J Psychiatry* 2004; 161: 217–22.
6. Cipriani A, Pretty H, *et al.* Lithium in the prevention of suicidal behaviour and all-cause mortality in patients with mood disorders: a systematic review of randomised trials.*Am J Psychiatry* 2005; 162: 1805–19.
7. Soares-Weiser K, Bravo Vergel Y, *et al.*. A systematic review and economic model of the clinical effectiveness and cost effectiveness of interventions for preventing relapse in people with effectiveness of interventions for preventing relapse in people with bipolar disorder. *Health Technol Assess* 2007; 11: 1–226.
8. Coryell W, Winokur G, *et al.* Lithium and recurrence in long term follow up of bipolar affective disorder.psychol med.1997;27:281-289.
9. Chan HH, Wing Y, *et al.*A control study of the cutaneous side effects of chronic lithium therapy. J Affect Disord. 2000 57:107–113
10. Bowden CL, Brugger AM, *et al.*, for the Depakoke Mania Study Group. Efficacy of divalproex vs lithium and placebo in the treatment of mania. JAMA. 1994;271:918-924.
11. Pope HG Jr, McElroy SL,*et al.*. Valproate in the treatment o acute mania: a placebo-controlled study. Arch Gen Psychiatry. 1991;48:62-68.
12. John R Geddes, Guy M Goodwin, *et al.* Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder(BALANCE): a randomised open-label trial. *Lancet* 2010; 375: 385–95
13. Charles L. Bowden, Joseph R.Calabrese, *et al.* A Randomized, Placebo-Controlled 12-Month Trial of Divalproex and Lithium in Treatment of Outpatients With Bipolar I Disorderfor Divalproex Maintenance Study GroupArch Gen Psychiatry. 2000;57:481-48
14. Lambert PA, Venaud G. Comparative study of valpromide versus lithium in the treatment of affective disorders. Nervure. 1992;5:57
15. Calabrese JR, Delucchi GA. Spectrum of efficacy of valproate in 55 patients with rapid-cycling bipolar disorder. AM J Psychiatry, 1990;147:431-434
16. McElroy SL, Keck PE Jr. Pope HG Jr. Sodium Valproate :its use in primary psychiatric disorders. J.clinPsychopharmacol. 1987; 7; 16-24.

17. Bowden CL, Ketter TA, Sachs GS, Thase ME. Focus on bipolar disorder treatment. J. Clin. Psychiatry.2005b; 66: 1598–1609.
18. FDA FDA approved drug products. 2009. [May 27]. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.
19. Fountoulakis KN, Grunze H, Panagiotidis P, Kaprinis G. Treatment of bipolar depression: an update. J Affect Disord. 2008; 109: 21–34.
20. Ketter TA, Wang PW, Nowakowska C, editors. Treatment of acute mania in bipolar disorder. American Psychiatric Publishing; Washington, DC: 2005.
21. Bowden CL. Acute and maintenance treatment with mood stabilizers. Int J Neuropsychopharmacol.2003;6: 269–75
22. Bowden CL. Predictors of response to divalproex and lithium. J ClinPsychiatry. 1995; 56(Suppl 3):25–30.
23. Swann AC, Bowden CL, *et al.* Depression during mania. Treatment response to lithium or divalproex. Arch Gen Psychiatry. 1997; 54: 37–42.
24. Kleindienst N, Greil W. Differential efficacy of lithium and carbamazepine in the prophylaxis of bipolar disorder: results of the MAP study. Neuropsychobiology . 2000;42(Suppl 1):2–10.
25. Lerer B, Moore N, Meyendorff E, *et al.* Carbamazepine versus lithium in mania: a double-blind study. J Clin Psychiatry. 1987; 48: 89–93.
26. Vasudev K, Goswami U, Kohli K. Carbamazepine and valproate monotherapy: feasibility, relative safety and efficacy, and therapeutic drug monitoring in manic disorder. Psychopharmacology (Berl) 2000;150:15–23.
27. Young RC, Biggs JT, *et al.* A rating scale for mania reliability, validity and sensitivity. Br.J Psychiatry. 1978; 133;429-435.
28. Hayes JF, Marston L, Walters *et al.*Lithium vs. valproate vs. olanzapine vs. quetiapine as maintenance monotherapy for bipolar disorder: a population-based UK cohort study using electronic health records. World Psychiatry. 2016 Feb; 15(1):53–8.
29. Severus E, Taylor MJ *et al.*Lithium for prevention of mood episodes in bipolar disorders: systematic review and meta-analysis. Int J Bipolar Disord. 2014 Dec 20; 2(1):15.

Source of Support: None Declared
Conflict of Interest: None Declared