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A Comparative Study between the Efficacy of Lithium with Sodium Valproate Combination Therapy and Lithium with Carbamazepine Combination Therapy in Patients with Euthymic Bipolar Disorder

Rajveer Singh Nirwan[1], Saravjot Kaur Sandhu[2], Rajendrakumar Katte[3]

[1]Junior Resident (P. G.3rd year), Department of Psychiatry, Pacific Institute of Medical Sciences, Udaipur (Rajasthan)

[2]Senior Resident, Department of Anaesthesiology, Dr. SS Tantia Medical College, Hospital and Research Center, Sri Ganganagar, Rajasthan, India
Email ID: *sandhusabinaz[at]gmail.com*

[3]Professor & Head, Department of Psychiatry, Pacific Institute of Medical Sciences, Udaipur (Rajasthan)

Abstract: ***Introduction: Treatment of bipolar disorder (BD) usually requires drug combinations. Lithium, sodium valproate and carbamazepine are each recommended as a monotherapy for preventing relapses in patients with bipolar disorders and are sometimes used in various combinations. However, Li/SVP and Li/CBZ combination have never been compared rigorously. Materials and methods: 70 patients aged 20 - 55 years diagnosed as bipolar disorder as per ICD 10 and euthymic for atleast 6 months - (HAM - D ≤8, YMRS≤6) who were on Lithium and sodium valproate combination therapy were chosen as group Li/SVP and on Lithium and carbamazepine combination therapy were chosen as group Li/CBZ. Functioning, quality of life, neurocognition and safety were assessed and compared between both groups. Results: Patients on Lithium and sodium valproate combination therapy had better GAF and WHOQOL - BREF score with statistically significant results (p<0.001). Also, the number of depressive and manic episodes were found to be reduced in the group receiving lithium and sodium valproate combination therapy. No between - group significant difference was found in neurocognition variables. Conclusion: Li/SVP combination therapy was found superior with better functioning and quality of life, lesser number of depressive and manic episodes in comparison to Li/CBZ combination therapy.***

Keywords: Bipolar disorder, Sodium valproate, Lithium, Carbamazepine

1. Introduction

Bipolar disorder (BD) is a disabling mental illness that is characterized by recurrentepisodes of mania, hypomania, depression, and mixed states separated by periods of relative euthymia.[1]Bipolar Affective Disorder (BPAD) being a complex episodic illness with high suicidality and comorbidity requires an equally complex pharmacologicaltherapy.[2]As a lifelong and recurrent illness, BD is associated with functional decline, cognitive impairment, and a reduction in quality of life (QOL).[3, 4, 5] During mania and depression epochs, bipolar patients show deficits in various cognitive domains[3], which can be explained by severe mood changes. Furthermore, some patients still experience cognitive impairment during euthymic epochs that can affect attention, executive function, and memory[3, 6], suggesting that cognitive dysfunction is not merely caused by the extreme mood during manic or depressed phases. Treatment of bipolar disorder conventionally focuses on acute stabilization, which aims to bring a patient with mania or depression to a symptomatic recovery with euthymic (stable) mood; and on maintenance, which aims to prevent relapse, reduction of subthreshold symptoms, and improve social and occupational functioning. Treatment options for management of Mood stabilisers, antidepressants, antipsychotic drugs, electroconvulsive therapy (ECT), supplementary medications, and psychosocial treatments can all be used as treatment options for BPAD management. Since many do not seem to respond to monotherapy, drug combinations are often recommended inspite of the presence of very little evidence.[7, 8] A possible strategy is to combine mood stabilizers, such as lithium plus sodium valproate (Li/SVP) and lithium plus carbamazepine (Li/CBZ).[9] These combinations are common in clinical practice and perform better than monotherapy in some patients with BD. However, their comparative efficacy is unknown.[10, 11]

However, the comparison between Lithium plus sodium valproate and Lithium plus carbamazepine combination therapy has been rarely done in the past. LICAVAL, a randomised trial was an important large study done that compared the efficacy and tolerability of Li/SVP and Li/CBZ in treating type 1 BD in young individuals. Since, there is paucity of literature in relation to studies comparing the efficacy of Lithium plus sodium valproate and Lithium plus carbamazepine combination in euthymic bipolar patients, this study has been done to compare the effectiveness of both the combination therapies.[12] Since, the literature is inconsistent on the effects of lithium plus sodium valproate and lithium plus carbamazepine combination therapy on cognitive functions in BPAD patients, this study also tries to compare neurocognition between both combination therapies.

Hence, under the light of above - mentioned data, the present study was undertaken for comparing efficacy of lithium plus sodium valproate combination therapy with lithium plus carbamazepine combination therapy in euthymic bipolar patients in terms of quality of life, functioning and cognition. In addition, treatment safety and tolerability were also compared between these two combination therapies.

2. Materials and Methods

After getting approval from institutional ethical committee, a hospital - based study was conducted on 70 patients diagnosed as bipolar disorder as per ICD 10 who were on lithium and sodium valproate combination therapy, as mood stabilizers were chosen as group Li/SVP (35 patients) and those diagnosed as bipolar disorder as per ICD 10 who were on lithium and carbamazepine combination therapy, as mood stabilizer were chosen as group Li/CBZ (35 patients). According to the inclusion and exclusion criteria, both groups were screened and included in the study. The study subjects were explained about the nature of the study and consent was obtained.

Patients who are diagnosed to have Bipolar Affective Disorder as per ICD - 10, between 20 - 55 years of age who have been euthymic for at least 6 months (HAM - D ≤8, YMRS≤6), have given written consent to participate. In the study, including attenders, have normal vision and hearing by history and clinical examination and who have been on Lithium and Sodium valproate as mood stabilizers and on Lithium and carbamazepine as mood stabilizers for at least 1 year are included in the study. Patients with other mental disorders, uncontrolled medical conditions, neurological disorders, learning difficulties and past history of ECT were excluded from the study.

Socio demographic details as per proforma were collected from groups Li/SVP and Li/CBZ. Complete physical examination including detailed Neurological evaluation was done. All subjects were then given the aforementioned scales and cognitive tests. Patients were in euthymia, defined as a HAM - D score of ≤8 and YMRS score of ≤6, for at least six months. Global assessment functioning (GAF) scale was used for rating the functioning of an individual, subjectively. The subjective well - being and QOL were assessed using the WHOQOL - BREF. The neurocognition assessment was done with the neuropsychological test battery which was directed at the following cognitive domains: executive functions (Stroop test, Trail making test - B, and FAB); working memory (Digit span backwards); attention (Digit span forwards and Trail making test - A). Udvalg for Kliniske Undersøgelser (UKU) Side Effect Rating Scale (UKU - SERS) was used for assessing treatment safety and tolerability.

The tests were given in a calm setting in a predetermined order in accordance with the usual administration guidelines. The time taken was about an hour to hour and 30 minutes. Assessments were conducted in 1 - 2 sessions, with each session lasting no longer than an hour.

Statistical design:
The data gathered as described above were used to create a statistical design.

Sample size calculation:
Prevalence: 1 - 1.6%
$n = z^2PQ/l^2$
z = 1.96
P = 0.015
Q = 0.985
l = 0.03
Output:
Sample size group Li/SVP – 35
Sample size group Li/CBZ – 35
Total sample size – 70

Statistics used:

All the results were recorded in Microsoft excel sheet and were subjected to statistical analysis using SPSS software (SPSS 22.00 for windows; SPSS inc. Chicago, USA). Group characteristics description and comparison was done using Chi - square test. Differences in mean scores between two groups was determined using Mann - Whitney U test and mean age of two groups was compared using student t - test. Spearman's Rank correlation was used to compare WHOQOL - BREF (each domain) with cognition variables and with other variables. The level of significance was set at $p < 0.05$.

3. Results

Among the patients of Li/CBZ group and Li/SVP group, 51.4 percent and 45.7 percent of the patients respectively were females while the remaining were males. In the Li/CBZ group, 54.3% were married, 31.4% were single - unmarried, 5.7% were separated from their spouses, 8.6% were widows/widowers. In the Li/SVP group, 54.3% were married (similar to the Li/CBZ group), 34.3% were single (slightly more than Li/CBZ group), 5.7% were separated from their spouses (similar to the Li/CBZ group), 5.7% lost their spouses (slightly lesser than Li/CBZ group).91.4% had completed primary or secondary education in group Li/CBZ, while in group Li/SVP it was 80%.8.6% in group Li/CBZ had done diploma or had a degree or were a postgraduate, while in group Li/SVP this comprised 20%. In group Li/CBZ, 42.9% were unemployed (included housewives), 57.1 % were employed. In group Li/SVP, 37.1% were unemployed (housewives also), and 62.9% were employed. The mean age in group Li/CBZ was 35.89 years and in group Li/SVP was 36.57 years. There was no significant difference between the age, gender distribution, marital status and education status between the two groups ($p>0.05$) (Table 1). Chi - square test was applied for the sociodemographic comparison between the two groups. p values for all categories were > 0.05, suggesting that there is no statistical significance between the two groups. Hence, the two groups were comparable with regards to the sociodemographic data. Student t - test was used to compare the mean ages of the two groups.

Table 1: Sociodemographic variables

Sociodemographic Variables	Li/CBZ		Li/SVP		Total	Chi - square value	p - value
	No. of cases	%age	No. of cases	%age			
Female (F)	18	51.40%	16	45.70%	34	0.229	0.632
Male (M)	17	48.60%	19	54.30%	36		
Total	35	100.00%	35	100.00%	70		
Married (m)	19	54.30%	19	54.30%	38	0.243	0.97
Single (s)	11	31.40%	12	34.30%	23		
Separated (sep)	2	5.70%	2	5.70%	4		
Widower (wr)	3	8.60%	2	5.70%	5		
Total	35	100.00%	35	100.00%	70		
Upto 8	19	54.30%	17	48.60%	36	0.243	0.391
Upto 12	13	37.10%	11	31.40%	24		
Graduate	3	8.60%	7	20.00%	10		
Total	35	100.00%	35	100.00%	70		
Unemployed	15	42.90%	13	37.10%	28	0.238	0.626
Employed	20	57.10%	22	62.90%	42		
Total	35	100.00%	35	100.00%	70		
Li/CBZ		Li/SVP		t	p - value		
Mean	SD	Mean	SD				
35.89	9.92	36.57	9.84	- 0.29	0.772		

Table 2: Frequency of depressive and manic episodes

		Li/CBZ		Li/SVP		Total	Chi - square value	p - value
		No. of cases	%age	No. of cases	%age			
Number of depressive episodes	0	19	54.30%	30	85.70%	49	11.777	0.003
	1	4	11.40%	4	11.40%	8		
	≥ 2	12	34.30%	1	2.90%	13		
Total		35	100.00%	35	100.00%	70		
Number of manic episodes	0	6	17.10%	17	48.60%	23	9.433	0.009
	1	9	25.70%	9	25.70%	18		
	≥ 2	20	57.10%	9	25.70%	29		
Total		35	100.00%	35	100.00%	70		

Using Chi - square test, ($p=0.003$), it was found that only 1 person (2.9%) in group Li/SVP had 2 or more depressive episodes following treatment, while 12 persons (34.3%) in group Li/CBZ had 2 or more depressive episodes.4 persons (11.4%) in group Li/SVP and group Li/CBZ had 1 depressive episode; while 19 people (54.3%) in group Li/CBZ and 30 (85.7%) people in group Li/SVP had no depressive episodes after administering the mood stabilizers. Also, it was found that 9 persons (25.7%) in group Li/SVP had 2 or more manic episodes following treatment, while 20 persons (57.1%) in group Li/CBZ had 2 or more depressive episodes.9 persons (25.7%) in group Li/SVP and group Li/CBZ had 1manic episode; while 6 people (17.1%) in group Li/CBZ and 17 (48.6%) people in group Li/SVP had

no manic episodes after administering the mood stabilizers. Thus, the number of depressive and manic episodes were found to be reduced in the group receiving lithium and sodium valproate combination therapy. A statistically significant (P<0.005) difference has been noted, suggesting that LI/SVP has been effective in reducing the number of episodes. (Table 2)

Table 3: Mean GAF score

	Li/CBZ		Li/SVP		Z	p - value
	Mean	SD	Mean	SD		
GAF	6.54	1.31	8.26	1.31	- 4.670	0.000

The mean GAF score in group Li/CBZ patients was found to be 6.54 with a standard deviation of 1.31while in group Li/SVP it was 8.26 with a standard deviation of 1.31. Clearly, GAF score has been found to be significantly better in the group Li/SVP (p<0.001). (Table 3)

Table 4: Comparison of WHOQOL - BREF domains between two groups

	Li/CBZ		Li/SVP		Z	p - value
	Mean	SD	Mean	SD		
WHOQOL - BREF physiological	50.60	17.49	76.60	13.55	- 5.359	0.000
psychological	51.49	17.92	74.34	18.27	- 4.588	0.000
social	56.86	18.69	76.86	15.35	- 4.189	0.000
environmental	58.14	18.16	76.03	15.10	- 3.963	0.000

Among the patients of group Li/CBZ mean WHOQOL - BREF physiological, psychological, social and environmental were 50.60, 51.49, 56.86 and 58.14 respectively. While among the patients of group Li/SVP mean WHOQOL - BREF BREF physiological, psychological, social and environmental were 76.60, 74.34, 76.86 and 76.03 respectively. On analysing statistically, it was seen that mean score of WHOQOL - BREF in each domain was significantly greater among the patients of group Li/SVP in comparison to the group Li/CBZ.

Table 5: Comparison of Cognitive variables between the two groups

	Li/CBZ		Li/SVP		Z	p - value
	Mean	SD	Mean	SD		
DF	4.54	1.22	4.49	1.42	- 0.06	0.952
DB	3.7	1.47	3.97	1.43	- 0.557	0.578
Stroop test time (sec)	270.71	55.5	283.03	48.77	- 1.093	0.275
FAB score total	14.83	3.45	14.74	3.22	- 0.185	0.853
FAB - similarities	2.77	0.49	2.57	0.56	- 1.751	0.08
FAB - lexical fluency	2.43	0.7	2.31	0.68	- 0.804	0.421
FAB - motor luria	2	0.87	2.03	0.92	- 0.187	0.852
FAB - conflicting instructions	2.4	0.77	2.54	0.74	- 0.855	0.393
FAB - go no go test	2.49	0.66	2.63	0.55	- 0.865	0.387
FAB - prehension behaviour	2.71	0.52	2.74	0.44	- 0.07	0.944
TMT - A: time (secs)	46.14	18.53	55.6	22.87	- 1.833	0.067
TMT - B: time (secs)	274.49	28.87	275.23	27.6	- 0.106	0.916

In this Mann Whitney U test has been used to compare the cognitive variables between the two groups. None of the results were significant as p> 0.05 for all the variables. Hence, the two groups were comparable with respect to cognitive variables. (Table 5)

Table 6: Side effects according to the UKU Side Effect Rating Scale

Side effects (S/E)	Total	Li/CBZ	Li/SVP	chi – square value	p – value
Diarrhea	10	8	2	4.200	0.040
Fatigue	14	2	12	8.928	0.003
Weight gain	44	14	30	15.664	0.001
Decreased sex drive	9	2	7	3.187	0.074
Aplastic anemia	3	3	0	3.134	0.077

While analysing, it was found that the Li/SVP group experienced greater frequencies fatigue (P = 0.040), weight gain (P = 0.001), and diminished sexual desire (P = 0.074). Aplastic anaemia (P=0.077) and diarrhoea (P=0.040) were more common in the Li/CBZ group.

4. Discussion

On literature research, there were not many studies available where lithium plus sodium valproate combination therapy was compared with lithium plus carbamazepine combination therapy in euthymic bipolar disorder patients. To our knowledge, the LICAVAL study[12] was done to compare the efficacy and tolerability of Li/VPA versus Li/CBZ in BD. Because there is limited literature on this subject, this study was conducted to assess the effectiveness, safety and tolerability of combination therapies using Li/SVP and Li/CBZ in euthymic bipolar disorder patients with regard to quality of life, functioning and cognition.

In our study, the socio - demographic variables were comparable among the two study groups and the difference was statistically non - significant (p>0.05). Similar results were in a study done by Sofia Brissos *et al.*[13]

We found that the number of depressive and manic episodes were found to be reduced in the group receiving lithium and sodium valproate combination therapy. A statistically significant (P<0.005) difference has been noted, suggesting that LI/SVP has been effective in reducing the number of episodes. (Table 2) The above results of our study are in line with the results seen study done by Xu *et al.*, who also found that in bipolar patients, rates of relapse were markedly lower in patients on the combination therapy when compared to

the monotherapies.[14] A study by Liu *et al.* also found that the combination of lithium and sodium valproate was more effective than the lithium monotherapy in relapse prevention.[15] This is supported by a study done by Neeli *et al.*[16] who reported that the number of episodes following treatment was found to be significantly reduced in the group receiving the combination therapy when compared to the group receiving monotherapy. Jin *et al.* in their meta - analysis, included six studies where lithium and valproate combination was compared with lithium monotherapy and the former was found to be associated with greater improvement in symptoms and lesser rates of remission.1[7]Similar results were found by other researchers too. In the BALANCE trial, remission occurred in around 45% of participants receiving Lithium and valproate combination in a 2 - year follow - up.[18] Also, Denicoff *et al.* reported marked/moderate CGI - BP improvement in around 55% of participants in one year.[19]Also, in the LICAVAL study, response and remission rates of 43.3% and 25% were found respectively in lithium plus valproic acid (Li/VPA) and lithium plus carbamazepine (Li/CBZ) group, and no significant between - group differences, which are in contrast to our results.[12]

In our study, functioning was assessed using Global Assessment Functioning scale (GAF) and quality of life was evaluated with World Health Organization Quality of Life Scale - Brief version (WHOQOL - BREF).

The mean GAF score in our study was found to be 6.54 with a standard deviation of 1.31 in group Li/CBZ while in group Li/SVP it was 8.26 with a standard deviation of 1.31. Clearly, GAF score has been found to be significantly better in the group Li/SVP ($p<0.001$). Our results are in contrary to BALANCE study as though the GAF was better in the combination therapy group, it was not found to be statistically.[18]Every domain of WHOQOL - BREF had a better score in group Li/SVP patients as compared to group Li/CBZ and the difference was significant ($p<0.001$) This is also in contradiction to BALANCE as though the quality of life was slightly better in the combination group, the difference was insignificant in the BALANCE study.[18] GAF score found to be positively correlated with the quality of life, i. e., more the GAF score, better was the quality of life.

In our study, it was found that none of the results were significant for all the neurocognitive variables ($p>0.05$) in both the groups. Thus, the two groups were comparable with respect to neurocognition. However, Li/SVP combination therapy fared better than the Li/CBZ combination therapy in the following tests - digit backward, FAB motor Luria, FAB conflicting instructions, FAB go - on - go test and FAB prehension behaviour though the results are insignificant. Though results were not statistically significant, FAB lexical fluency was found to be worse in the combination therapy which is supported by the study done by Vasile *et al.* who reported that lithium was found to be associated with decreased verbal fluency but this could be accounted for by the use of valproate which is associated with slowing of reaction time, memory and minor learning deficits.[20]The same study reported lower motor performance memory, [20] which contradicts our study results, in which FAB - motor luria, conflicting instructions and digit backward were performed better by the Li/SVP combination group, though the differences are not statistically significant.

According to the UKU Side Effect Rating Scale, the Li/SVP group had higher frequencies of fatigue ($P = 0.040$), weight gain ($P = 0.001$), and decreased sexual desire ($P = 0.074$). The Li/CBZ group had increased rates of diarrhea ($P = 0.040$) and aplastic anemia ($P= 0.077$). No reports of Li - associated neurological, thyroid, or renal adverse events were seen. These results are in line with the LICAVAL study done by Giovani Missio *et al.*[12]

5. Conclusion

On the basis of our study, we infer that the quality of life of those euthymic bipolar patients on the combination therapy of lithium and sodium valproate was found to be better than those on the lithium and carbamazepine combination therapy. Every domain of WHOQ0L - BREF - physiological, psychological, social and environmental were found to be better in those receiving the lithium and sodium valproate combination therapy than the lithium and carbamazepine combination therapy. The functioning of those euthymic bipolar patients on the lithium and sodium valproate combination therapy was found to be better than those on the lithium and carbamazepine combination therapy. There was no difference in the cognitive domains tested memory, attention and executive functions between the two groups. The number of manic and depressive episodes following treatment were found to be much lesser in those receiving the lithium and sodium valproate combination therapy. Thus, Li/SVP combination therapy was found superior with better functioning and quality of life, lesser number of depressive and manic episodes in comparison to Li/CBZ combination therapy.

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Conflicts of interest
There are no conflicts of interest.

References

[1] Muller - Oerlinghausen B. Berghofer A, and Bauer M. Bipolar disorder. Lancet.2002; 359 (9302): 241.
[2] Kessing LV, Hellmund G, Geddes JR, Goodwin GM, Andersen PK. Valproate v. lithium in the treatment of bipolar disorder in clinical practice: observational nationwide register - based cohort study. The British Journal of Psychiatry.2011 Jul; 199 (1): 57 - 63.
[3] Martínez - Arán A, Vieta E, Colom F, Reinares M, Benabarre A, Gastó C, Salamero M. Cognitive dysfunctions in bipolar disorder: evidence of neuropsychological disturbances. Psychotherapy and psychosomatics.2000; 69 (1): 2 - 18.
[4] Michalak EE, Yatham LN, Lam RW. Quality of life in bipolar disorder: a review of the literature. Health and quality of life outcomes.2005 Dec; 3 (1): 1 - 7.
[5] Bonnin CM, Sanchez - Moreno J, Martinez - Aran A, Sole B, Reinares M, Rosa AR, Goikolea JM, Benabarre A, Ayuso - Mateos JL, Ferrer M, Vieta E. Subthreshold symptoms in bipolar disorder: impact on

neurocognition, quality of life and disability. Journal of affective disorders.2012 Feb 1; 136 (3): 650 - 9.
[6] Miskowiak KW, Burdick KE, Martinez-Aran A, Bonnin CM, Bowie CR, Carvalho AF, Gallagher P, Lafer B, López-Jaramillo C, Sumiyoshi T, McIntyre RS. Methodological recommendations for cognition trials in bipolar disorder by the International Society for Bipolar Disorders Targeting Cognition Task Force. Bipolar Disorders.2017 Dec; 19 (8): 614 - 26.
[7] Goodwin GO, Consensus Group of the British Association for Psychopharmacology. Evidence - based guidelines for treating bipolar disorder: revised second edition—recommendations from the British Association for Psychopharmacology. Journal of Psychopharmacology.2009 Jun; 23 (4): 346 - 88.
[8] Bipolar disorder [Internet]. National Institute of Mental Health. U. S. Department of Health and Human Services; [cited 2023Jan18]. Available from: https: //www.nimh. nih. gov/health/topics/bipolar - disorder
[9] Grande I, de Arce R, Jiménez - Arriero MA, Lorenzo FG, Valverde JI, Balanza - Martinez V, Zaragoza S, Cobaleda S, Vieta E. Patterns of pharmacological maintenance treatment in a community mental health services bipolar disorder cohort study (SIN - DEPRES). International Journal of Neuropsychopharmacology.2013 Apr 1; 16 (3): 513 - 23.
[10] Keck PE, McElroy SL. Carbamazepine and valproate in the maintenance treatment of bipolar disorder. Journal of Clinical Psychiatry.2002 Jan 1; 63: 13 - 7.
[11] Granneman GR, Schneck DW, Cavanaugh JH, Witt GF. Pharmacokinetic interactions and side effects resulting from concomitant administration of lithium and divalproex sodium. The Journal of clinical psychiatry.1996 May 1; 57 (5): 204 - 6.
[12] Missio G, Moreno DH, Demetrio FN, Soeiro - de - Souza MG, dos Santos Fernandes F, Barros VB, Moreno RA. A randomized controlled trial comparing lithium plus valproic acid versus lithium plus carbamazepine in young patients with type 1 bipolar disorder: the LICAVAL study. Trials.2019 Dec; 20 (1): 1 - 9.
[13] Brissos S, Dias VV, Kapczinski F. Cognitive performance and quality of life in bipolar disorder. The Canadian journal of psychiatry.2008 Aug; 53 (8): 517 - 24.
[14] Xu W, Wang X, Chen C. Effect and safety of combination therapy of valproate with lithium on recurrent mania. Chinese Journal of Psychiatry.2007; 40 (2): 86.
[15] Liu, Y., Liu, W., Zhu, W. and Sun, L. A comparative study of lithium carbonate combined with sodium valproate in the prevention of bipolar disorder. Journal of Psychiatry.2007; 20: 89 - 90.
[16] Neeli Uma Jyoti, Mounica Bollu, Faizan Ali, Sri Chaitanya, M. Chiranjeevi. Lithium and sodium valproate combination therapy versus monotherapy in treatment of bipolar disorders: an observational cohort study. European Journal of pharmaceutical and medical research.2015, 2 (3): 614 - 619
[17] Jin W, Uscinska M, Ma Y. Review of double mood stabilizer treatments for bipolar disorder in China. Open Journal of Psychiatry.2014 Jan 3; 2014.
[18] Geddes JR, Goodwin GM, Rendell J, Azorin JM, Cipriani A, Ostacher MJ, Alder N, Morriss R, Juszczak E. Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open - label trial. Lancet.2009 Dec 23; 375 (9712).
[19] Denicoff KD, Smith - Jackson EE, Disney ER, Ali SO, Leverich GS, Post RM. Comparative prophylactic efficacy of lithium, carbamazepine, and the combination in bipolar disorder. Journal of Clinical Psychiatry.1997 Nov 15; 58 (11): 470 - 8.
[20] Vasile D, Vasiliu O, Mangalagiu AG, Ojog DG. EVALUATION OF THE MOOD - STABILIZERS ASSOCIATED NEUROCOGNITIVE EFFECTS IN BIPOLAR PATIENTS. Therapeutics, Pharmacology & Clinical Toxicology.2011 Dec 1; 15 (4).