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Open Label, Switch Over, Two Phased, Comparative Efficacy Trial Between Sodium Valproate and Magnesium Valproate in Patients of Bipolar Disorder

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ABSTRACT

The present study aimed to compare efficacy between sodium valproate and magnesium valproate in patients of bipolar disease. The study was done at department of psychiatry at NSCB Medical Hospital, it was of 1 year and number of patient recruited after detailed examination and considering inclusion and exclusion criteria were 60. It was an open label, switch over, two phased comparative study where each patient first received 1000 mg of sodium valproate for 15 days, after that efficacy assessment was done. In the second phase patient was switched over to magnesium valproate where intially750 mg of magnesium valproate was given and again after 15 days 1250 mg of magnesium valproate was given and efficacy was assessed. Patients were evaluated for efficacy by Youngs Mania Rating Scale (YMRS), BPRS and CGI. Statistical analysis was done by using SPSS18. It was found out that both salts of valproic acid were equally efficacious as both causes significant reduction (p<.0001) in YMRS, CGI and BPRS, though reduction is highest for 1250 mg magnesium valproate followed by1000 mg of sodium valproate and lastly for 750 mg of magnesium valproate.

KEYWORDS sodium valproate, magnesium valproate, bipolar disorder

introduction

Bipolar disorder, also known as manic-depressive illness, is a brain disorder that causes unusual shifts in mood, energy, activity levels, and the ability to carry out day-to-day tasks.

Bipolar disorder is defined by the presence of one or more episodes of mania lasting for at least 7 days or hypomania lasting for at least 4 days with or without one or more depressive episodes.Bipolar disorder often develops in a person's late teens or early adult years. At least half of all cases start before age 25.People with bipolar disorder experience unusually intense emotional states that occur in distinct periods called "mood episodes." An overly joyful or overexcited state is called a manic episode, and an extremely sad or hopeless state is called a depressive episode. Sometimes, a mood episode includes symptoms of both mania and depression. This is called a mixed state. People with bipolar disorder also may be explosive and irritable during period of manic episode .The disorder has been subdivided into bipolar I, bipolar II, cyclothymia, and other types, based on the nature and severity of mood episodes experienced; the range is often described as the bipolar spectrum.Since its discovery by John Cade[1], lithium remains the benchmark treatment for acute mania. It was approved by the U.S. Food and Drug Administration (FDA) in the 1970s for treatment of mania.For more than 30 years, lithium has been the drug of choice for the treatment of bipolar disorder. However, it has numerous adverse effects, a relatively slow onset of action, many common drug-drug interactions, and a narrow therapeutic index. Because of these problems, researchers looked for alternative and adjunctive treatments in bipolar disorder, focussing on the anticonvulsants valproate and carbamezepine[2].Valproic acid or divalproex sodium (Depakote), approved by the FDA in 1995 for treating mania, is a popular alternative to lithium for bipolar disorder.

The efficacy of valproate in the treatment of acute mania was proved by 16 non-controlled studies and 6 controlled studies. Valproate was comparable to lithium in a 12-week RCT of acute mania[3] and superior to lithium in a double blind trial of patients with mixed episodes[4].As a rule, the results indicate that valproate was efficient in nearly 60% of the cases, including those which had unsatisfactory response to lithium, showing higher results than those with placebo and comparable to those with lithium[5,6]. Mixed episodes have also good acute and prophylactic responses with valproate[7].The following factors were described as predictors of good response in the treatment of acute mania with valproate, these are : the presence of depressive symptoms, diagnosis of mixed episodes, rapid cycling[8], with alcohol abuse, substance abuse, mental retardation, and antecedents of head trauma and neurological lesions[9].Patients with comorbidity with anxiety disorders and type II bipolar depressed patients may show satisfactory response[10].Several open studies suggested its efficacy in the prophylactic treatment of manic and depressive episodes, with responses in nearly 63% of assessed patients[7] .Valproate is available clinically in a number of forms: these include sodium valproate alone, valproic acid alone, and sodium valproate in combination with valproic acid and magnesium valproate. Magnesium valproate among them is the newest form, it was formulated and clinically used as anticonvulsant in Argentina in 1971. There are very few studies comparing the sodium and magnesium salt of valproic acid. Efficacy and tolerability study in the patients of seizures have shown that both salts are equally efficacious[11]. Pharmacokinetic studies comparing both salts have shown that magnesium valproate has lesser inter individual variability and therefore it offers additional advantages in comparison with sodium valproate[12]

Materials & Methods

Study Area

The study was performed at the Department of Pharmacology in collaboration with Department of Psychiatry NSCB Medical College, Jabalpur, where patients are offered outpatients consultation & hospital admission when necessary.

Selection of Cases
The participants were of 18 years of age & provided written informed consent before any study procedure was initiated.

Inclusion Criteria
- DSM –IV criteria for bipolar disorder.
- There should not be any past history or physical disorder that would likely to deteriorate during participation
- There should be not abnormal blood platelet count or transaminases level.
- Should be able to communicate in Hindi/English.

EXCLUSION CRITERIA
- Patients requiring ECT.
- Patient with hypertension,cardiac disorder, medical or neurological disorder other than epilepsy.
- Pregnant/ Nursing females.
- Patients with suicidal tendency.
- Unable to provide informed consent.
- History of hypersensitivity to Valproate.
- Patients with hepatic or renal impairment.
- Patients requiring frequent medication changes.
- Patients on antipsychotic medication.
- Patients unable to comply with study protocols or patients who are unwilling.

The duration of study was of one year. The total no. of patient taken in study were 60. Before including in the study each patient underwent detailed psychiatric neurological & medical examination. A detailed proforma was made to assess the patient. Each patient/patients relative should be given written consent to participate in the study.

The study was an open label, switch over, two phased comparative study. In the study, each patient first received 1000 mg of sodium Valproate for 15 days. After this period, an assessment regarding efficacy was taken into account.

Then in the second phase two different doses that is 750 mg & 1250 mg was given, again each for 15 days. After the end of both dosing schedules, assessment regarding efficacy was done.

The patient was evaluated on Young Mania Rating Scale (YMRS)[13]. It is one of the most frequently utilized rating scales to assess manic symptoms. The scale has 11 items, there four items that are graded on a 0 to 8 scale (irritability, speech, thought, content, & disruptive behaviour, while the remaining seven items are graded on a 0-4 scale. typical YMRS baseline scores vary a lot, they depend on patient clinical feature such as mania (YMRS = 12), depression (YMRS=3, 0 or euthymia (YMRS=2)

The BPRS Developed by JE Overall and DR Gorham[14] having 18 items is perhaps the most researched instrument in psychiatry. All items are rated on a seven point scale (1= not present, 7= most severe).

The limitations include somewhat ambiguous criteria for various levels of severity; strength of scale includes its brevity, ease of administration wide use and well researched status.

Reliability coefficients of 0.56 to 0.87 have been reported by the authors.

CGI developed by National institute of Mental Health refers to Global impression of the patient and requires clinical evaluation of the syndrome under assessment. The CGI measures overall illness severity and response to treatment in psychiatric illness.

There are seven categories of severity ranging from "1=Not ill" to "7=extremely ill" improvement is also rated on a seven point spectrum "1= very much improved" to "7=very much worse" The CGI takes less time is simple, and clinically understandable. It is very sensitive scale and is an established measure of efficacy in clinical trials.

STATISTICAL ANALYSIS
The data of the present study were recorded into the computers and after its proper validation, check for error, coding & decoding were compiled and analysed using the software SPSS 18 for windows. Appropriate univariate and bivariate analysis were carried out using the Student t test for the continuous variable (age) and paired t-test for repeated measures (i.e. 0, 15, 30 and 45th day observations) or chi-square ($\chi 2$) test for categorical variables (side effects). All means are expressed as mean ± standard deviation. The critical levels of significance of the results were considered at 0.05 levels i.e. $P < 0.05$ was considered significant.

Efficacy results:
TABLE 1 showing YMRS scale profile during each visit

		Mean	SD	N	Significance
Pair 1	YMRS-0	14.22	4.183	60	t=14.682; p<0.0001
	YMRS-15	9.40	3.669	60	
Pair 2	YMRS-0	14.22	4.183	60	t=11.954; p<0.0001
	YMRS-30	10.77	3.693	60	
Pair 3	YMRS-0	14.22	4.183	60	t=17.819; p<0.0001
	YMRS-45	7.93	3.374	60	

This table shows YMRS scores comparisons of 15th, 30th,45th day with the day 0 i.e. Baseline.

The mean Baseline YMRS Score was 14.22(±4.183), which dipped to 9.40(±3.669). So, the mean improvement over first 15 days of sodium valproate is 4.82 or 34%.

When compared to baseline, the 30th day mean of YMRS was 10.77(±3.693). The Mean improvement is 3.45 or24.5%, however when compared with 15th day mean it worsening of the mean by 1.37.

The 45th day mean was 7.93(±3.374), with improvement from the baseline of 6.29 or 44.2%.

The t- scores for all the three pairs is highly significant with p<0.000

TABLE 2 showing CGI Severity Score profile during each visit

		Mean	SD	N	Significance
Pair 1	SEVER-O	4.72	.904	60	t=9.017; p<0.0001
	SEVER-15	3.80	.659	60	
Pair 2	SEVER-O	4.72	.904	60	t=6.779; p<0.0001
	SEVER-30	4.15	.732	60	
Pair 3	SEVER-O	4.72	.904	60	t=12.317; p<0.0001
	SEVER-45	3.52	.770	60	

This table shows CGI severity scores comparisons of 15th, 30th, 45th day with the day 0 i.e. Baseline.

The mean Baseline CGI severity Score was 4.72(±.904), which dipped to 3.80(±.659). So, the decrease in severity over first 15 days of sodium valproate is .92 or 19.5%.

When compared to baseline, the 30th day mean of CGI was 4.15(±732). The Mean improvement was .57 or 12%, however when compared with 15th day mean it worsening of the mean by .35.

The 45th day mean was 3.52(±.770), with improvement from the baseline of 1.2 or 25.4%.

The t- scores for all the three pairs is highly significant with p<0.0001

TABLE 3 showing CGI Improvement Score Profile during each visit

		Mean	SD	N	Significance
Pair 1	IMPRO-0	.00	.000	60	t=29.514; p<0.0001
	IMPRO-15	3.02	.792	60	
Pair 2	IMPRO-0	.00	.000	60	t=35.433; p<0.0001
	IMPRO-30	3.70	.809	60	
Pair 3	IMPRO-0	.00	.000	60	t=22.841; p<0.0001
	IMPRO-45	2.65	.899	60	

This table shows CGI improvent scores comparisons of 15th, 30th ,45th day with the day 0 i.e. Baseline.

At baseline the improvement assessment was not applied.

The mean scores of 15th, 30th, and 45th day were 3.02, 3.70, and 2.65 respectively.

The t- scores for all the three pairs is highly significant with p<0.0001

TABLE 4 showing BPRS Score Profile during each visit

		Mean	SD	N	Significance
Pair 1	BPRS-0	26.97	4.603	60	t=13.295; p<0.0001
	BPRS-15	22.33	3.467	60	
Pair 2	BPRS-0	26.97	4.603	60	t=13.429; p<0.0001
	BPRS-30	23.37	3.787	60	
Pair 3	BPRS-0	26.97	4.603	60	t=15.135; p<0.0001
	BPRS-45	20.85	3.359	60	

This table shows BPRS scores comparisons of 15th, 30th,45th day with the day 0 i.e. Baseline.

The mean Baseline BPRS Score was 26.97(±4.603) which dipped to 22.33(±3.467). So, the decrease in severity over first 15 days of sodium valproate was 4.64 or 17.6%.

When compared to baseline, the 30th day mean of BPRS was 23.37(±3.787). The Mean improvement is 3.6 or 13.3%, however when compared with 15th day mean it worsening of the mean by 1.04.

The 45th day mean was 20.85(±3.359), with improvement from the baseline of 6.12 or 22.7%

The t- scores for all the three pairs is highly significant with p<0.0001

Discussion

In this open label, cross over study final analysis was done in 60 recruited patients of bipolar disorder.All the patients were initially received 1000mg of sodium valproate for the first 15 days. Most of the patients showed improved response. They showed 35% improvement in YMRS score. Also, there was 17% improvement in BPRS score and decreased severity in CGI score by 20%.After 15 days patients were crossed over to receive magnesium valproate in two different doses i.e750 mg for the first 15 days and 1250 mg for the next 15 days. It was seen that in the first 15 days with magnesium valproate improvement seen prior halts a bit. YMRS dipped to 25% improvement, as compared to 35% in case of sodium valproate. Similar responses were seen in CGI severity i,e from 19% severity decrease to 12% severity decrease, and in BPRS score from 18% dip to 13% .When the dose of magnesium valproate was increased, improvement was once again seen. YMRS score soon rose again to 45%. CGI severity decreased to 25%, also BPRS score increased to 23%. Compared to initial mean YMRS 14.22(±4.183), the end point mean YMRS was 7.93(±3.374), showing significant improvement.

Similar improved results were obtained in CGI severity and BPRS scale.

The initial mean CGI severity and BPRS were 4.72(±.904) and 26.97(±4.603) respectively and the end point readings were 3.52(±.770) and 20.85(±3.359).

The mean YMRS at the 15th and 30th day were 9.40(±3.669) & 10.77(±3.693).

The mean CGI severity and BPRS scales on 15th day were 3.80(±.659) & 22.33(±3.467) after the cross over mean values changed to 4.15(±732). & 23.3 (±3.787).

It was due to difference in doses that the improvement varies in the two phases. On increasing the dose of magnesium valproate, not only it compensates the decreases trend, but it supersedes the responses of sodium valproate.In respect with above findings, we can say that both salts of valproate are equally efficacious.

Summary and conclusion

- Total number of patient recruited was 60.
- In our study 42% patients were in the age group 20-30. Bipolar disorder is more common in younger people.
- The mean age in male patients is 32.6, in female patients the mean age was 30.52(±9.30).
- The male to female ratio of study was 1.61:1
- 58.3% patients were married and 41.7% patients were unmarried.
- 63.4% of patients belong to the rural areas.
- 14 patients were dropped out during the study.
- Overall drop out rate in our study was 19%.
- Drop out due to loss of follow up was more common in patients from rural areas.
- 3 patients have highly elevated liver enzymes investigated on 15th day, so they were withdrawan from the study due to risk of hepatic failure.
- Both the salts of valproic acid are equally efficacious. both of these causes significant reduction(P<.0001) in the YMRS , BPRS and CGI Severity, though the reduction is highest for the 1250 mg of magnesium valproate, followed by 1000 mg of sodium valproate and lastly to the 750 mg sodium valproate.

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