Dr. A.K. Kala award

Comparative study of olanzapine versus divalproex in acute treatment of bipolar disorder : A 3-week prospective study

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Abstract

Introduction: *Bipolar disorder is a devastating condition with wide-reaching negative consequences. Treatment guidelines, while often varied, commonly emphasize the use of mood stabilizers and atypical antipsychotics in the treatment of bipolar mania.* ***Objective:*** *To study the efficacy and tolerability of olanzapine and divalproex in the treatment of Bipolar affective disorder in a 3-week randomized prospective study.* ***Methods:*** *A 3-week, randomized, prospective study compared flexibly dosed olanzapine (5–30 mg/day) with divalproex (500– 2500 mg/day in divided doses) for the treatment of patients hospitalized for the management of bipolar manic or mixed episodes. The Young Mania Rating Scale and the Hamilton Depression Rating Scale were used to quantify manic and depressive symptoms, respectively. Safety was assessed with several measures.* ***Results:*** *The protocol defined baseline to endpoint improvement in the mean total score on the Young Mania Rating Scale as the primary outcome variable, which decreased by 16.5 for patients treated with olanzapine and 12.0 for those treated with divalproex. Of the sample, 93.3% of olanzapine-treated patients showed response as compared to 66.7% of divalproex treated patients; 40% of olanzapine-treated patients demonstrated remission compared to 26.7% of divalproex-treated patients. The average weight gain with olanzapine treatment was 2.4 kg compared to 1.07 kg with divalproex treatment.* ***Conclusion:*** *No significant difference was observed in olanzapine and divalproex treatment group in the mean improvement on young mania mania rating scale and protocol-defined remission and response.*

Keyword: *Bipolar Disorder, Olanzapine, Divalproex.*

Introduction

Bipolar disorder is a devastating condition with an estimated prevalence of 0.1%–2% among adolescents[1–3] and 2.4% among adults worldwide.[1] Significant morbidity is associated with bipolar disorder, with wide-reaching negative consequences such as poor academic performance, disruptions in family and social relations, substance abuse, hospitalizations, and a high rate of mortality because of suicide.[2,3,6,7] In 1972, lithium was approved by the U.S. Food and Drug Administration (FDA) for the treatment of acute mania. More than 20 years elapsed before the next drug, divalproex, was

approved. More recently, olanzapine, a thio-benzodiazepine previously approved for treatment of psychotic disorders, was the third drug approved by the FDA for treatment of acute mania.[8] Both divalproex[9,10] and olanzapine[11,12] have demonstrated acute antimanic efficacy in two placebo-controlled, parallel-group trials.[8]

Treatment guidelines, while often varied, commonly emphasize the use of lithium, divalproex, and atypical antipsychotics in the treatment of bipolar mania.[13,14] Olanzapine is an atypical antipsychotic with proven efficacy in the treatment of bipolar mania in the acute and maintenance settings.[11-15]

Atypical antipsychotics have more favourable side effect profiles[6,7] and as a class, recent evidences have shown their efficacy in mania as a combination therapy.[8,9] Research has indicated that antipsychotics may be useful in patients with bipolar and affective disorders. Antipsychotics plus a mood stabilizer was more efficacious than a mood stabilizer alone, and was well tolerated.[4,10-13] Presence or absence of psychosis had no significant effect on anti-manic property of antipsychotics.[4]

The primary aim of the present study was to compare the efficacy and safety of olanzapine versus divalproex in the treatment of manic or mixed episode of bipolar affective disorder over a 3-week period.

Methods

Patients

A total of 30 consecutive patients aged between 18 to 65 years with a diagnosis of bipolar affective disorder, manic or mixed episode, with or without psychotic features, as per ICD-10 criteria (WHO, 1992) who gave informed consent for the study were enrolled. A minimum total score of 20 on the Young Mania Rating Scale (YMRS) [16] was required on the day of random assignment to study groups (baseline). Patients were excluded if they had a serious/unstable medical illness, substance dependence as per ICD-10 within past 30 days (except nicotine and caffeine), Intolerance and non- responsive to olanzapine and divalproex in the past, had undergone treatment with elcetro-convulsive therapy within previous 24 hours, had suicidal risk or were preganant/ lactating. Patients who were on medications like lithium, anticonvulsants or antipsychotic medications within the last one week were also excluded.

Study design

It is a 3 week, open label, randomized, comparative, parallel group study conducted on indoor patients of the Department of Psychiatry, GMCH, Chandigarh. In this study, a total of 30 patients were recruited and they were randomly assigned to either Group 1 (olanzapine group) or Group 2 (divalproex group). Patients in group 1 received olanzapine (5–20 mg/day) and Group 2 received divalproex (500–2500 mg/day). All the patients were hospitalized at least for the first week of the treatment. The initial daily doses were 15 mg/day of olanzapine and 1500 mg/day of divalproex. Investigators made dose adjustments primarily on the basis of clinical response but also on the basis of adverse events. Patients who did not tolerate the minimum baseline dose (5 mg/day olanzapine or 500 mg/ day divalproex) were discontinued from the study.

Concomitant use of lorazepam was restricted to a maximum dose of 2 mg/day and administration was not allowed within 8 hours of the administration of a symptom rating scale. In case of extrapyramidal symptoms, trihexy-phenydil upto maximum dose of 6 mg/day was permitted. Trihexyphenydil for the prophylaxis of extra-pyramidal symptoms was not allowed.

Assessments

Patients were assessed for the symptoms and the severity of illness with 11-item Young Mania Rating Scale (YMRS)[16] and the 21-item Hamilton Depression Rating Scale (HAM-D).[17] The assessments were done at the baseline, daily for the first week during admission and at week 2 and week 3 thereafter. The improvement in the patients were categorised as Symptomatic remission and Clinical response. Symptomatic remission was defined as endpoint YMRS total score d"12 and clinical response was defined as e"50% baseline-to-endpoint reduction in YMRS score.[8]

Safety was assessed by monitoring adverse events, as well as by monitoring laboratory tests values (includes Haemogram, Renal function tests, Liver function tests, Fasting Blood Sugar, Lipid profile), ECG results, changes in weight, and scores on Simpson-Angus Scale for the extrapyramidal symptoms.[18] Adverse events that originally occurred or worsened in severity during this study were considered treatment emergent and recorded. Extrapyramidal symptoms and adverse events were recorded at week 1, 2 and 3. Laboratory tests, weight and ECG were recorded at baseline and week 1, 2 and 3.

Statistical Analysis

Patient data was analysed on Intent to treat basis using Pearson Chi-square test, likelihood ratio and linear by linear ration. Efficacy and EPS rating scale scores were evaluated by Analysis of Variance.

Results

A total of 33 patients were initially recruited for the study, of which one patient discontinued treatment due to adverse effects of divalproex. Two patients did not follow up after a week of admission period. As their follow-up assessments were not available, they were excluded from the study. A final sample of 30 patients was reached, with each 15 patients each in olanzapine and divalproex group.

Nearly 50% (7/15) of the patients in the olanzapine group were 21-30 years of age while 40% (6/15) of patients in divalproex group were 31-40 years of age. The two groups were comparable in age distribution (table 1). There were 4 females in divalproex group as compared to 2 females in olanzapine group. No statistically significant difference was found in both the groups regarding the socio-demographic variables like marital status, education, religion and family type.

Table 1: Age-wise distribution of study groups

Age	Study groups†	
	Olanzapine (n=15)	Divalproex (n=15)
10-20 yrs	02	02
21-30 yrs	07	02
31-40 yrs	02	06
41-50 yrs	02	02
51-60 yrs	—	03
> 60 yrs	02	—

†p=0.082; Statistical analysis by chi-square test

On the basis of diagnosis, patients were categorised as Bipolar affective disorder, manic episode; Bipolar affective disorder, mixed episode and Bipolar affective disorder, manic episode with psychotic symptoms (table 2).

Table 2: ICD-10 Diagnosis of study groups

Diagnosis	Study groups†	
	Olanzapine (n=15)	Divalproex (n=15)
BPAD- manic episode	08	07
BPAD- mixed episode	01	02
BPAD-manic episode with psychotic symptoms	06	06

†p=0.183; Statistical analysis by chi-square test

The mean of duration of current episode was 36.67 days and 32.73 days in olanzapine and divalproex group respectively, as shown in table 3.The mean YMRS score at baseline in olanzapine and divalproex group were 31.07 and 32.93 respectively and both the groups were comparable in the severity (Table 3).On comparison of onset of improvement of the illness based on the reduction in YMRS score, significant improvement was seen in olanzapine group from day 5 (p = 0.026), while in case of divalproex group, it was seen from week 2 (p<0.01) as shown in Table 5.

Response and Remission

Clinical response, characterised as e"50% improvement in the YMRS score at endpoint, was achieved by 93.3% of olanzapine-treated patients and 66.7% of divalproex-treated patients but the difference in response rate was not statistically significant in this study (p=0.169, Fisher's exact test) as shown in table 5. However, among responders, the estimated time-to-response was earlier in the olanzapine group. The rates of symptomatic remission (endpoint YMRS total score d"12) were 40.0% in the olanzapine treated patients and 26.7% for the divalproex treated patients which was also not statistically significant (p=0.700, Fisher's exact test) as shown in Table 5.

The percentage change in YMRS score in both groups was not significant statistically.

Table 3: Duration of current episode and YMRS scores

	Study groups		
	Olanzapine (n =15)	**Divalproex (n=15)**	p
Duration (in days)	36.67 ± 16.11	32.73 ± 14.06	0.48
YMRS score	31.07 ± 3.35	32.93 ± 6.23	0.69

Statistical analysis by Independent samples t- test

Table 4: Improvement in YMRS Score

Study Group	**Day of assessment (n^{th})**	**Mean Difference (Day n^{th} - Day 1^{st})**	**SE**	**p**	**95% CI**	
					Lower Bound	**Upper Bound**
Olanzapine	2	-.200	1.205	1.000	-3.44	3.04
	3	-1.133	1.205	.913	-4.38	2.11
	4	-2.400	1.205	.242	-5.64	.84
	5	-3.533	1.205	.026*	-6.78	-.29
	6	-4.333	1.205	.003*	-7.58	-1.09
	7	-5.467	1.205	<.001*	-8.71	-2.22
	8	-11.467	1.205	<.001*	-14.71	-8.22
	9	-18.267	1.205	<.001*	-21.51	-15.02
Divalproex	2	-.133	2.162	1.000	-5.95	5.68
	3	-.533	2.162	1.000	-6.35	5.28
	4	-1.867	2.162	.943	-7.68	3.95
	5	-2.600	2.162	.761	-8.42	3.22
	6	-3.333	2.162	.512	-9.15	2.48
	7	-4.667	2.162	.174	-10.48	1.15
	8	-10.533	2.162	<.001*	-16.35	-4.72
	9	-16.333	2.162	<.001*	-22.15	-10.52

Table 5: Improvement in YMRS scores

	Study groups (N=15 each)		
	Olanzapine	**Divalproex**	**p**
Number of patients (with >50% improvement at endpoint)	14 (93.3%)	10 (66.7%)	0.169
Number of patients (with YMRS < =12 at endpoint)	06 (40.0%)	04 (26.7%)	0.700

Statistical analysis by Fischer's exact test

Weight gain

Patients in the olanzapine treatment group had a larger mean weight gain, compared to the patients in the divalproex treatment group (mean weight gain at week 3 was 2.4 kg and 1.07 kg respectively) (Table 6).

Table 6: Weight changes (gain) in the study groups

Drug	**Time**	**Weight gain (mean)**	**p**
Olanzapine	Week 1	0.400	0.999
	Week 2	1.533	0.974
	Week 3	2.400	0.911
Divalproex	Week 1	0.133	1.000
	Week 2	0.800	0.997
	Week 3	1.067	0.993

The mean of percentage weight change in both groups was statistically significant with mean as 4.02 and 1.71 in olanzapine and divalproex group respectively (p=0.001), as shown in table 7.

Table 7: Percentage change in weight

	Study groups (N=15 each)		
	Olanzapine	**Divalproex**	p
% change in weight	4.024 ± 1.819	1.715 ± 1.446	0.001*

Adverse Events

Adverse drug checklist was used to find out the common side effects caused by these drugs. Common complaints reported by patients in olanzapine group were sedation, dry mouth, hypotension and increased appetite, while in divalproex group, dizziness and nausea were the more frequent complaints.

Extrapyramidal symptom

The Extrapyramidal symptoms (EPS) were found more in the olanzapine group mostly in the form of tremors, rigidity, increased salivation and gait disturbances. Five of the patients in olanzapine group had EPS as compared to 2 in divalproex group. The severity of EPS was more in first group for which trihexyphenidyl was used. The difference in occurrence of EPS in the two groups was statistically significant at week 1 (Z=2.106; p=0.035) and week 3 (Z=2.278; p=0.023).

Vital signs

There were no statistically significant differences between treatment groups in the

incidence rates of potentially clinically relevant changes in vital signs. No changes in the ECG done on weekly basis were noted in any of the patient of both groups.

Laboratory measures

There were no significant between- group differences in rates of treatment-emergent abnormalities in the hemogram, renal function tests and fasting blood sugar levels. Some changes in the liver function tests in form of raised SGPT and SGOT levels of few patients were noted in the olanzapine group, but these changes were not significant.Apart from this, no significant findings were noted in the levels of Lipid Profile and Body Mass Index of patients in both the groups.

Discussion

The study aimed to compare the efficacy and tolerability of olanzapine and divalproex in patients of Bipolar Affective Disorder. Although olanzapine has earlier onset of action as indicated by reduction in YMRS score, but the overall efficacy at the endpoint of 3 weeks was comparable in both the groups and not statistically significant. Some of the earlier studies support these findings,[19, 21] while few others showed olanzapine more efficacious than divalproex.[8,20] In a study by Tohen et al[19] olanzapine and divalproex had similar effects at 3 weeks but olanzapine was better at 12 weeks.

A report recently presented by Zajecka et al[21] described a study comparing divalproex sodium (N= 63) to olanzapine (N=57) in the treatment of acute mania. The authors used a starting loading dose of 20 mg/kg per day for divalproex sodium (mean maximum dose=2115 mg/day) and 10 mg/day for olanzapine (mean maximum dose=14.7 mg/day). As in the present study, statistically similar improvement in the YMRS was observed in both the groups. Similarly Tarr et al 2008[20] reported in a meta-analysis that monotherapy with second generation antipsychotics demonstrates statistically significant advantages over mood Stabilizers in terms of both efficacy and acceptability, and may be preferable for initial choice of treatment during the acute phase of illness.

In a recent 4-week, placebo-controlled trial that used 15 mg/day of olanzapine as the starting dose,[12] the mean reduction in the YMRS score at week 3 was 13.9 points while it is 16.5 point reduction for olanzapine-treated patients in the current trial. While in divalproex treated patients, the mean reduction in YMRS score at endpoint is 12.0 in our study. Few available data address whether the 12.0-point mean improvement in the divalproex group is in line with expectations. A placebo-controlled valproate trial reported by Pope et al[10] used the YMRS as the primary outcome variable, but the results may not be directly comparable to those of the current trial because the Pope et al study enrolled lithium-refractory and/or intolerant patients. In that 3-week study, 17 valproate-treated patients had a mean improvement on the YMRS of 11.4 points, almost same as observed in the current study.

The response rates for both the treatment groups in our study (olanzapine 93%; divalproex 67%) are higher than those previously reported for acute treatment of bipolar disorder. In two placebo-controlled studies of 3-week and 4-week duration, the response rates (e”50% decrease from baseline to endpoint in YMRS score) in the olanzapine treatment group were 49% and 65%, respectively.[11,12] In another 3-week study comparing olanzapine and divalproex, the response rate of the olanzapine treatment group was 54% versus 42% in divalproex treatment group.[8] Tohen et al[22]

compared olanzapine and haloperidol, and reported that the response rate in the olanzapine group was 72% after 6 weeks of treatment versus 74 % in the haloperidol group. The higher response rates in our study may be explained by certain limitations in our study and the most important being the smaller sample size. Certain patient's characteristics like the type of episode (type of onset, mixed type, cycling pattern etc) and the response rate in our population might be different from the western countries due to phenotypic and genotypic differences.

The mean increase in weight of patients in both the treatment groups at endpoint (olanzapine- 2.4 kg; divalproex – 1.06 kg) was significant in our study. Tohen et al 2002[8] also reported that patients in the olanzapine treatment group (mean=2.5 kg) had a significantly larger mean weight gain, compared to the patients in the divalproex treatment group (mean=0.9 kg). The mean weight gain with olanzapine treatment over 3-4 weeks had previously been reported in the range of 1.65 kg to 2.5 kg with a greater susceptibility observed among children and adolescents.[25-28]

The significant weight gain observed during this short, 3-week trial raises concerns about potential health consequences of prolonged treatment with olanzapine, particularly in the proportion of patients who experienced rapid weight increase[11, 14, 24] Tohen et al 2007 [7] reported in their study that although the probability of responding is good, the probability of gaining weight is even greater. The benefits of olanzapine for treatment of BPAD should be considered within the context of its safety profile as observed in this study. In our study, an increase in the level of liver enzymes (alanine transaminase and aspartate transaminase) at 3 weeks in olanzapine group were noted which were also reported in previous studies.[11, 12, 29]

Similar increases in alanine transaminase and aspartate transaminase values have been observed in adult patients treated with olanzapine,[11,12] although they appear to be asymptomatic and transient in nature.[29] Furthermore, the long-term consequences of these increases in liver enzymes in adolescents are unclear and further studies to evaluate the same are needed for better understanding.

Tohen et al[19] 2008 reported olanzapine was significantly more efficacious than placebo but not better than divalproex at 3 weeks. But at 12 weeks, olanzapine was significantly more efficacious than divalproex at 12 weeks. But olanzapine-treated patients had significantly greater increase in weight and in glucose, cholesterol, triglyceride, uric acid, and prolactin levels than divalproex-treated patients at 12 weeks.[19] Therefore, before starting olanzapine straight away in situations where other good options are available, the above mentioned consequences should be kept in mind to avoid serious metabolic side effects in patients.

To Conclude, both olanzapine and divalproex has similar efficacy in the treatment of acute phase of Bipolar Affective Disorder (mania, mixed state) as shown by significant reduction in YMRS scores at end of the study. The response and remission rates in both the groups were comparable. Olanzapine has early onset of action then divalproex. Both the drugs were well tolerated. However, the patients in olanzapine treatment group experienced more adverse events, have statistically significant more mean weight gain and have more increase in the level of aspartate and alanine transaminase liver enzymes.

From the findings of the study, we can have three options for the management of Bipolar Affective Disorder:

(a) In acute first episode of mania, olanzapine can control the symptoms in a very short period and thus can reduce

the need of hospitalization, thereby reducing the cost of treatment.

(b) In cases where psychiatrist prefer to use combination of Antipsyochotic Drugs and mood stabilizers, the Antipsychotic Drugs can be discontinued within 2 weeks because by that time, the effect of mood stabilizer (divalproex) starts and thus we can minimize the risk of Antipsyochotic Drugs induced metabolic side effects.

(c) The study also shows that all the patients of Bipolar Affective Disorder (mania, mixed state) may not need concomitant use of antipsychotic drugs because the mood stabilizers alone can have adequate clinical response, though it is delayed. In this scenario, the risk of metabolic syndrome induced by the antipsyochotic drugs can be avoided.

The clinicians should consider all these options and choose the appropriate strategy in the individual case.

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