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Original article

Valproate-Risperidone versus Valproate-Lithium combination in acute mania

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ABSTRACT

Background: We evaluated the efficacy of valproate plus risperidone versus valproate plus lithium combination in the treatment of acute mania.

Methods: In 2-week, randomized, double-blind, parallel group study, 46 acute manic patients according to DSM-IV criteria were randomly assigned to receive combination of valproate 20 mg/ kg/day plus risperidone 2-4 mg/day (n=23) or lithium600-1200 mg/day (n=23). The assessment of efficacy measures were according to Young Mania Rating Scale (YMRS) and Clinical Global Impressions-Severity (CGI-S) and Improvement (CGI-I) scale. Other effectiveness measures included YMRS response (YMRS reduction $\geq$50 %) and YMRS remission (YMRS total scores $\leq$12).

Results: In each group, 16 of 23 patients (70 %) completed the study. YMRS response, CGI-Improvement, and reduction in the total scores of YMRS and CGI-S observed in both groups, significantly greater for valproate-risperidone than valproate-lithium combination group (P=0.006, P=0.015, P=0.004, and P=0.007, respectively).YMRS remission were shown in both groups without statistical significance (P=0.073). The total scores of YMRS at 4th, 8th, and 14th days of trial were lower in valproate-risperidone than valproate-lithium combination group (P=0.017, P=0.005, and P=0.004, respectively). The rate of adverse events and mean weight gain in both groups were not statistically different.

Conclusion: In acute manic patients, both combinations of valproate with lithium or with risperidone had efficacy in acutely manic patients, but valproate-risperidone combination was more effective. Both treatments were safe and well tolerated. Considering the small sample size and limited period of observation, further studies need to be conducted to find out the best combination in the treatment of acute mania.

Key words: Acute mania, Valproate, Risperidone, Lithium, Combination Therapy

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Bipolar mood disorder (BMD-I) is a common mental illness. The risks of morbidity and mortality of its intense manic episodes often requires hospitalization and rapid controlling of impulsivity, aggression, irritability, agitation, and psychotic symptoms. The primary goals of treatment for mania are to accelerate behavioral restoration as quickly as possible to decrease dangerousness to self and others, and limit the costs of manic episodes [1].

For swift control of acute mania, adjunctive agents including combinations of two mood stabilizers or of a mood stabilizer with an antipsychotic agent are broadly used[2-4] .Typical antipsychotics are commonly used in combination with mood stabilizers for acute mania. Beside the effectiveness of typical antipsychotics, they lead to side effects such as induction of depressive symptoms and tardive dyskinesia [5].

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Atypical antipsychotics have more favorable side effect profiles [6, 7] and as a class, recent evidences have shown their efficacy in mania combination therapy [8, 9].

Researches have indicated that risperidone may be useful in patients with bipolar and affective disorders. Risperidone 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 antimanic property of risperidone [4].

There are also evidences to suggest that combination of lithium and valproate is an effective treatment strategy for patients who did not respond to lithium or valproate alone [14, 15]. This combination can reduce hospitalization period and need to other adjunctive, which has already been proven to be safe and effective in long term treatment of patients with bipolar disorder [2, 3].

Even though, there are no controlled clinical trials on valproate-lithium, this combination is widely used for treatment of acute mania [16]. Furthermore, only few randomized, double-blind, and adequately controlled studies were done to compare the safety and efficacy of an atypical antipsychotic plus a mood stabilizer versus combination of two mood stabilizers.

In this study, the efficacy, response rate, and side effects of risperidone plus valproate have been compared with lithium plus valproate.

Subjects and Methods

This 2-week, double-blind, randomized, parallel-group study was done in Noor University hospital, Isfahan, Iran at 2003. Its protocol was approved by the board review of Behavioral Sciences Research Center, Isfahan University of medical sciences.

Patients were 18-65 years old with BMD-I most recent episode manic, hospitalized for treatment in Noor psychiatric emergency center, Isfahan, Iran. An expert psychiatrist diagnosed BMD-I(manic episode) based on DSM-IV and the Composite International Diagnostic Interview (CIDI)[17]. A minimum score of 20 and maximum score of 50 on the Young Mania Rating Scale (YMRS) [18] also was needed. Patients had to be medically stable according to physical examination, medical history, electrocardiography and laboratory data. After complete description of the study for them, written informed consent was obtained.

Exclusion criteria were another DSM-IV axis I diagnosis except substance abuse; use of mood stabilizers within 72 hours before hospitalization; known sensitivity to risperidone, lithium or sodium valproate; history of severe extrapyramidal side effects and history of response to another treatment regimens in past episodes. Also, laboratory values (liver, renal and thyroid function tests) outside the normal range; history of clinically significant medical diseases; pregnancy; lactation and childbearing potential (without adequate contraception) excluded the patients from the study.

Data from patients who missed before forth day of the study or whose management was changed due to any problem, were not analyzed.

Eligible patients who met selection criteria were randomly assigned to receive sodium valproate plus risperidone or lithium. In both groups, patients received 20 mg/kg per day sodium valproate (Minoo Co. Iran) three times daily at the days 1-14.

In the first group, risperidone (Bakhtar Bioshimi Iran) was administered once daily in 2 mg capsules (matching those capsules used for lithium) at the days 1-2, and twice daily at the days 3-14.

In the second group, lithium capsules [300 mg, which produced from lithium tablets (Iran Darou)] were administered three times daily at the days 1-5. If the patient's body weight was below 45 Kg, lithium was used twice daily. After measuring serum lithium concentration at the days 5 and 10, if lithium level was below 0.8mEq/L, the dosage of lithium was adjusted by 300 mg increment in dosage at the days 6 and 11.

Total number of placebo capsules (matched for lithium and risperidone) were equally administered per day for each patient in both

groups. In addition to the main drugs, only 1 to 4 mg/day oral clonazepam (Sobhan Darou Iran) or lorazepam (Wyeth-Ayerst Lab USA) were permitted to be administered during the trial. For severe agitation, intramuscular lorazepam was allowed.

During the double-blind phase, YMRS was evaluated at admission, 4th, 8th, and 14th day by a trained blind psychiatry resident. The primary effectiveness measure was the change in the mean of YMRS scores from baseline to endpoint. The next effectiveness measures included "YMRS response", (a reduction of 50% or more in YMRS scores) [8-13, 19] and "YMRS remission" (defined as YMRS $\leq$ 12) [8, 13].

The Clinical Global Impressions–Severity (CGI-S) scores were assessed at admission and 14th day [20]. Also, Clinical Global Impressions–Improvement (CGI-I) scale score was assessed at the end of study [20].

Patients were evaluated for any adverse events based on vital signs, physical examination and direct questions. Liver function test, hematology and biochemistry tests were performed at admission and the day 14. Thyroid function tested at admission. Electrocardiography was done on admission and the day 3. Serum level of lithium was measured at the days 5 and 10.

SPSS software statistically analyzed the data, using unpaired T-test, Mann-Whitney, Wilcoxon Signed ranks and Chi-square tests. All statistical tests were two-tailed with a significance level of 0.05 (P-value < 0.05).

Results

Within 59 patients, 46 cases were enrolled in two groups, equally. During the study, a total number of 7 patients (30.4%) dropped out in each group: between 4th and 7th days, four patients (17.4%) discontinued the trial in each group; in group 1, three patients missed due to withdrew consent and one due to cardiac complication (increased QT interval). In group 2, all missing rate were due to withdraw of consent.

Between 8th and 14th days, 3 patients (13.0%) dropped out in each group; two of them in group 1 missed due to withdraw of consent and one due to loss of response. In group 2, one patient missed due to withdraw of consent, one due to gastrointestinal complication (severe vomiting), and another one due to loss of response. The missing rate and time of missing in both groups were not statistically different.

Both groups were similar in demographic and baseline characteristics with no statistically significant difference (Table 1).

Table1. Demographic features and baseline characteristics of disease.

Adverse events (%)	Valproate Risperidone (n=23)	Valproate Lithium (n=23)	Fisher's Exact Test
Somnolence	26.1	27.2	1.000
Tremor	21.7	9.0	0.218
Nausea	17.4	27.2	0.475
Dizziness	17.4	13.6	0.681
Vomiting	8.7	13.6	0.636
Dyspepsia	8.7	27.2	0.120
Diarrhea	4.3	9.0	0.550
Extra pyramidal	4.3	0.0	0.312
Urinary frequency	0.0	4.5	0.312

[a] All values greater than 0.05 show no statistically significant differences between groups.
M=male; F=female; YMRS=Young Mania Rating Scale.

The mean length of hospitalization was 12.0 days for group 1 and 11.8 days for group 2, which their difference did not reach statistical significance.

During the study, the mean dose of benzodiazepine used for each patient were 2.61and 3.63 mg/day in group1 and 2, respectively, which had no statistical difference (P=0.259).

The total rate of adverse events was 65.2% in group 1 and 54.5%in group2. Chi-squared test showed no statistically difference between groups (P=0.465). The adverse events were listed in Table 2.

The mean weight of the patients at admission in group 1 and 2 were 64.6 kg (SD=11.2) and 64.9 kg (SD=11.8), respectively. The mean weight at endpoint were 66.0 kg (SD=11.8) and 65.6 kg (SD=11.5). The weight gain in both groups was not statistically different (P=0.898).

Table 2. The incidence of adverse events

	Valproate-Risperidone N (%)	Valproate- Lithium N (%)	TOTAL N (%)	Fisher's Exact Test[a]
Male/Female	14/9(61/39)	11/12(48/52)	25/21(54/46)	0.554
Presence of substance abuse	13 (57)	8 (35)	21 (46)	0.118
Family history of mood disorder	8 (35)	8 (35)	16 (35)	0.754
Presence of psychotic features	22 (96)	19 (83)	41 (89)	0.321
	Mean (SD)	Mean (SD)	Mean (SD)	T test p-value
Age (year)	29.8 (10.3)	31.4 (10.1)	30.6 (10.1)	0.604
Weight(kg)	64.6 (11.7)	64.9 (11.8)	64.8 (11.4)	0.938
Mean YMRS on admission (day)	31.5 (7.2)	30.8 (6.0)	31.2 (6.6)	0.740
Duration of disorder(year)	5.5 (6.0)	5.7 (5.7)	5.6 (5.8)	0.907
Previous manic episodes	3.8 (4.1)	2.7 (1.9)	3.3 (3.2)	0.260
Hospitalizations (day)	3.0 (4.3)	1.9 (1.3)	2.5 (3.2)	0.234

The mean daily dose of valproate in group 1 was 1173mg (SD=178) and in group 2 was 1164mg (SD=146) which showed no statistically significant difference (P=0.854).

The mean serum lithium concentration in group 2 at 5th and 10th days of study was 0.51mEq/l (SD=0.10) and 0.72mEq/l (SD=0.17) respectively.

The mean total scores of YMRS in both groups at baseline and through consecutive measures were shown in Table-3. Wilcoxon test showed that the changes of YMRS scores at 14th day from baseline in each group were statistically significant (P<0.001).

By considering CGI, changes in severity (CGI-S) scores in both groups were statistically significant (P< 0.0009 in group 1 and P=0.001 in group 2). In group 1, all subscales of YMRS had statistically significant changes from baseline to endpoint of the trial (P< 0.05).In group 2, all subscales of YMRS except appearance and sex items changed at 14th day of the study from the beginning, significantly (P<0.05).

The nonparametric Mann-Whitney test revealed that group 1 had significantly greater improvement in total YMRS scores at 4th, 8th and 14th days compared with group 2(P = 0.017, P = 0.005 and P= 0.004, respectively). Also, changes of YMRS scores from baseline to 4th, 8th and 14th days were significantly more evident in group 1 than in group 2 (P<0.001, P=0.004 and P=0.004, respectively) (Table 3 and Figure 1).

In group 1 and 2, 93.7% and 43.7% of patients showed 50% or more reduction in YMRS, respectively which had statistically significant difference (P=0.006). In group 1, 75% of patients reached the remission threshold (YMRS≤12) whereas in group 2, 37.5% met this index without statistically significant difference (P=0.073).

The mean changes in severity of mania on CGI-S demonstrated significantly more decrease in group 1 than in group 2(P=0.007).In group one, 68.75% of patients were rated as "much improved" or "very much improved" on the CGI-I scale, compared to 31.25% of group 2(P=0.015).

YMRS subscale scores which were significantly different between two groups included sleep (P=0.012), continuity of thought (P=0.007), appearance (P=0.037), and insight (P=0.021) at 8th day and sleep (P=0.010), speech (P=0.041), content of thought (P=0.020), and appearance (P=0.022) at 14th day.

Table 3. Efficacy results at baseline, 4th, 8th, and 14th days and mean changes between the days

	Valproate- Risperidone		Valproate-Lithium		Analysis
Efficacy variable	N	Mean (SD)	N	Mean (SD)	
Baseline YMRS	23	31.5(7.2)	23	30.8(6.0)	0.740[d]
YMRS at 4th day	23	19.9(5.4)	23	24.0(5.8)	0.017[d]
YMRS at 8th day	19	13.5(5.8)	19	19.6(6.8)	0.005[d]
YMRS at 14th day	16	9.6(5.5)	16	16.3(6.6)	0.004[d]
YMRS CHANGE between:					
4th day and baseline	23	-11.6(5.2)	23	6.8(2.2) -	0.0009[e]
8th day and baseline	19	-17.7(7.0)	19	-12.1(3.8)	0.004[e]
14th day and baseline	16	-21.4(8.0)	16	-14.4(3.8)	0.004[e]
8th and 4th day	19	-6.1(3.4)	19	-4.9(2.8)	0.244[e]
14th and 4th day	16	-9.4(4.2)	16	-7.4(3.0)	0.129[e]
14th and 8th day	16	-3.4(1.9)	16	-2.9(2.1)	0.548[e]
YMRS remission (%) [a]	16	75	16	37.5	0.073[f]
YMRS response (%) [b]	16	93.7	16	43.7	0.006[f]
CGI severity CHANGE between: 14th day and baseline	16	2.6(1.0)-	16	-1.6(1.1)	0.007[e]
CGI global improvement response (%) [c]	16	68.75	16	31.25	0.015[f]

[a] YMRS score≤12.
[b] ≥50% decrease from baseline in the YMRS total score.
[c] proportion of patients 'much' or 'very much' improved.
[d] p-value by independent-samples T Test
[e] Mann-Whitney Test
[f] Fisher's Exact Test (chi-square)

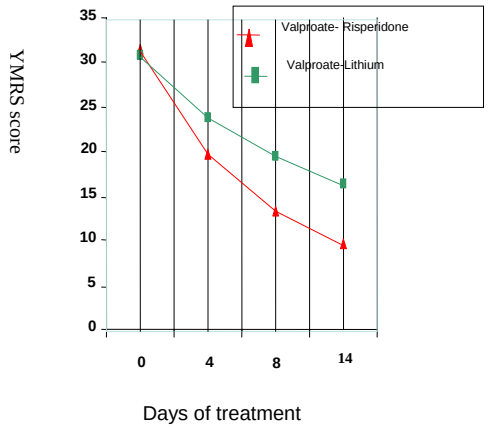

Figure 1. Decline of YMRS score at 4th, 8th, and 14th days from baseline.

Discussion

Both valproate-risperidone and valproate-lithium combinations were safe and tolerable treatments, but valproate-risperidone combination was more effective than the other.

Combination of valproate and risperidone was assessed in some clinical trials which revealed safety and effectiveness of this treatment for acute manic Patients [4, 10-13, 21-23].

In two studies comparing mood stabilizer alone and risperidone plus mood stabilizer, the antimanic effectiveness of 'added on' risperidone was reported at first week[4, 22]. In a prospective pilot study, Tohen et al treated 15 bipolar manic patients with psychotic features by risperidone plus mood stabilizer and showed 78% YMRS response rate after 2 weeks [23] which in our study, it was 97.3%.

Vieta et al find 87% in YMRS response rate after 6 weeks treatment by mood stabilizer plus risperidone, the YMRS response rate. Of course, 84.2 % of patients demonstrated 'much' or 'very much' improvement in CGI-I scores[19]. In our trial, 68.75 % of patients showed such improvement in CGI-I scores. The difference between these two studies was probably due to shorter duration of our trial.

Although risperidone induced exacerbation of manic symptoms in some earlier isolated case or series reports, there was no sign of such

effect in patients treated by risperidone in this trial. Those studies had several confounding factors and their patients received only risperidone without any mood stabilizers [4, 11, 19]. Risperidone efficacy in the treatment of mania was independent of antipsychotic effects, as decreased YMRS total scores were not correlated only to psychotic subscales of YMRS. Such result was observed previously by Sachs et al [4].

In a review of safety and efficacy of mood stabilizers combination for bipolar disorder, valproate-lithium combination was found as the most efficacious and safest combination treatment strategy[24]. However, as Zarate and Quiroz stated, there were no controlled clinical trials about combination of valproate plus lithium even though used widely for treatment of acute mania[16].

Findling et al demonstrated that YMRS response rate in young bipolar patients with valproate-lithium combination was 70.6 % and improvement in CGI-I scores were 59.3% after 8 weeks[14]. However in adult patients YMRS response was 25% and YMRS remission was 50% in the study of Calabrese et al [25]. In our study YMRS response in valproate-lithium combination group was 43.7% and improvement in CGI-I scores was 31.25%. These findings are comparable but lower than those presented by Findling et al[14] which probably was due to shorter duration of our study.

In valproate-lithium group, although the mean serum lithium levels at 5th and 10th days were below the optimal therapeutic level (0.8-1.2 mEq/L), but they were comparable to this index in another study (0.77mEq/L) [8]. Nevertheless, the effect favoring risperidone over lithium may reflect modest dosing with lithium in this group.

Although each of these treatment strategies by themselves had sustained efficacy during the period of the study, the valproate-risperidone group showed significant improvement in YMRS total scores and YMRS changes at all assessments, especially in the 4th day of the trial. Thus, valproate-risperidone might decrease the duration of hospitalization by accelerating YMRS response and facilitate treatment in less restrictive settings.

The comparison of two combination strategies also showed that YMRS response, CGI-I, reduction in the total scores of YMRS and CGI-S were significantly greater in valproate-risperidone than in valproate-lithium group at the end point of the trial.

Generally, both treatment strategies were well tolerated. Only one patient in each group dropped out because of severe adverse events. The rate of adverse events in both group had no significant difference.

According to Sachs et al, the most common adverse event in valproate-risperidone combination group was somnolence[4]. In the valproate-lithium group, somnolence, nausea, and dyspepsia were the most common adverse events in our study and emesis, enuresis, and stomach pain in Findling et al study [14].

The mean weight gain was not significantly different between two groups which were against finding of Sachs et al in 3 week study of risperidone-mood stabilizer combination [4].

This trial had several limitations including short duration of study; lack of serum valproate level measurement, and patient drop out due to withdrew consent. The limited settings of Noor emergency center could not permit the investigators to continue the trial more than two weeks. For ethical reasons, although patients were permitted to leave the study, but the efficacy measures were so prominent that the results are likely clinically meaningful.

In conclusion, considering small sample size and limited and period of observation, further studies need to be conducted to find out the best combination in treatment of acute mania.

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