

### Sodium valproate as an adjunctive to trifluoperazine in the treatment of schizophrenia

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**Abstract:** There are controversies regarding sodium valproate efficacy in schizophrenia. Although some studies have reported that it is effective in the treatment of positive symptoms and aggression in schizophrenia, others have not found such an association. Our study aims to investigate the effects of as an adjunctive valproate in the pharmacological treatment of patients with schizophrenia. **Methods:** In a clinical trial, 22 schizophrenic patients (age 18 – 65), were randomly allocated into two groups. The first group was treated by combination of valproate and trifluoperazine and the other by trifluoperazine alone. A diagnosis of schizophrenia was established based on DSM-IV-TR criteria. The collected data on the 1<sup>st</sup>, 14<sup>th</sup> and 28<sup>th</sup> days of the admission by PANSS test and were analyzed by Paired T tests through SPSS. **Results:** Comparison of PANSS mean score in two groups, before and after the trial, showed statistically differences. There was a statistically significant reduction in positive symptoms in the group treated with valproate plus trifluoperazine than trifluoperazine alone after 2 weeks of treatment; the difference was also significant in the fourth week. **Conclusion:** Our study shows that valproate can do as an adjunct to antipsychotic drug in the treatment of positive symptom of schizophrenia.

[Hashemi Mohammad Abad N, Ghaffarian Shirazi HR, Mohammadi A, Kashkouli Behroozi M, Hosseini Mehrian Z. **Sodium valproate as an adjunctive to trifluoperazine in the treatment of schizophrenia.** *J Am Sci* 2013; 9(10s):60-62]. (ISSN: 1545-1003). <http://www.jofamericanscience.org>. 10

**Keywords:** Trifluoperazine, Schizophrenia, sodium valproate.

#### Introduction

Schizophrenia is a mental disorder which the persons unable to understand the reality. It most commonly manifests itself as hallucinations, delusions, or disorganized speech and thinking, and it leads to significant social or occupational dysfunctions. The onset of symptoms occurs typically in young adulthood or at early puberty. (1)

Schizophrenia is diagnosed based on either the self-reported experiences, or abnormalities in behavior reported by family members, friends or colleagues, followed by a clinical assessment by a mental health professional or a psychiatrist. The assessment includes the medical- psychological record and testing the patient's mental condition. (2). There are two standard criteria used for diagnosis of schizophrenia: American Psychiatric Association (DSM-IV-TR) criteria – used in the United States, and the ICD-10 criteria- World Health Organization- used mostly in European countries. Based on DSM-IV-TR criteria at least two of the following at one month duration must be met: Delusions, hallucinations, disorganized speech, obvious catatonic or disorganized behavior, avolition, alogia or blunted affect. Positive symptoms are: hallucinations, delusions, bizarre behavior, and positive formal behavior. Negative symptoms are:

affective flattening, alogia, avolition-apathy, anhedonia(3). A typical fact in patients diagnosed with schizophrenia is a high increase of the dopamine function in the mesolimbic pathway of the brain. The primary treatment for schizophrenia is antipsychotic medication. This type of medication reduces the dopamine function (4). The treatment of Schizophrenia is often assessed using standard methods such as Positive and Negative Syndrome Scale (PANSS). For severe episodes, hospitalization may occur either voluntarily or involuntarily (5). Main effect of antipsychotic medication can be seen in approximately 7 to 14 days. Antipsychotics can reduce negative symptom and especially the positive symptoms of psychosis. Though, the newer antipsychotics have significantly made the negative symptoms better. Although the Sodium Valproate is basically an anticonvulsant, but nowadays it is commonly used in the treatment of various mental disorders for example schizophrenia. Some studies showed that valproate with antipsychotic drugs is effective on aggression and positive symptom of schizophrenia (6-11). However, some researchers showed that valproate is not more effective than placebo in controlling psychotic symptoms in schizophrenia (4 and 12-14).

In this study we will investigate the effect of sodium valproate combine with trifluoperazine in the treatment of schizophrenia.

### Method and Materials

This research is a double blind randomize controlled parallel trial to measure the effect of valproate adjunct to trifluoperazine on the treatment of schizophrenia. The samples consisted of the schizophrenic patients referred to Shahid Mofateh Clinic of Yasouj City (south of Iran) during 2011-2012. The inclusion criteria were the age limit of 15-65, having schizophrenic diagnosis by DSM-IV-TR and psychiatrist diagnosis, no antipsychotic drug use, no pregnancy. Exclusion criteria were pregnancy on the study period, uncooperative patient and patients' family. 24 patients participate to the study but 2 patients had no cooperated and finally 22 patients were till the end of study. Patients were randomly assigned to two groups (experimental and control) by randomized block design, each group consist of 11 patients. Experimental group were on valproate (200-600 mg/day) with trifluoperazine (5-30 mg/day) and control group on trifluoperazine alone (5-30 mg/day). The optimal dose of trifluoperazine and valproate were decided by psychiatry evaluation. Severity of psychosis, efficacy and side effect of antipsychotic drug was measured with PANSS (positive and negative syndrome scale) by psychiatrist at 1<sup>th</sup>, 14<sup>th</sup> and 28<sup>th</sup> day. This research was carried out by a financial support from the Vice Chancellor for Research of Yasouj University of Medical Sciences. Informed consent was also obtained from the patients. The collected data were analyzed by SPSS, independent T test and paired T test.

### Results

The current study was conducted on 22 patients with schizophrenia who referred to Shahid Mofatteh Clinic of Yasouj city (south of Iran). These 22 patients included 18 men (82%) and 4 women (18%). 12 patients were married (54%) and 10 patients were single (45%). 14 patients (28%) were 20-30 years old (the most). The youngest patient had 19 years old and the oldest one had 60 years old. Mean age of statistics community was 38.3 years. The patients divided to two groups: experimental and control group (every group were 11 patients). 3 patients of experimental and 1 patient of control group were female and others were male. 3 patients (13%) were illiterate and not able to write and read, 9 patients (40%) had education lower than diploma and only 10 patients (45%) had diploma or higher education. Minimum and maximum applied doses were between 5 and 30 mg/day (based on psychiatrist evaluation). Minimum and maximum applied dose of valproate were between 200 to 600 mg/day (based on psychiatry evaluation). The effect of valproate with trifluoperazine on positive symptom of schizophrenic patients is more effective than trifluoperazine alone, at 14<sup>th</sup> and 28<sup>th</sup> of evaluation to 1<sup>th</sup> day (by statistical analysis), but there is no good effect from 28<sup>th</sup> to 14<sup>th</sup> day of evaluation. There is no good effect on negative symptom and general symptom at any day of evaluation (by statistical analysis) (table 1).

### Discussion

Schizophrenia has been considered as a major disease entity over the past century, occurs in all populations. It is characterized by an admixture of positive, negative, cognitive, mood, and motor symptoms.

Table 1: Comparison of positive, negative, general and global symptom in experimental group and control group at 1<sup>th</sup>, 14<sup>th</sup> and 28<sup>th</sup> day of treatment.

Sign and symptom		First day evaluation	14 <sup>th</sup> day evaluation	28 <sup>th</sup> day evaluation
Positive symptom	Experimental group	76/27±13/81	36/27±13/81	27/27±13/81
	Control group	73/17±14/18	69/17±18/31	68/24±12/25
	T test	NS	S	S
general symptom	Experimental group	74/27±13/83	54/27±13/62	43/27±12/87
	Control group	75/17±15/16	55/17±11/27	41/14±25/11
	T test	NS	NS	NS
Negative symptom	Experimental group	66/27±13/28	52/27±13/14	41/27±13/21
	Control group	71/17±14/18	51/13±23/17	39/17±17/28
	T test	NS	NS	NS
global symptom	Experimental group	72/27±13/84	47/27±13/84	37/27±13/84
	Control group	72/97±12/15	58/97±13/45	49/97±15/16
	T test	NS	S	S

There are various antipsychotics drugs for treatment of schizophrenia. Many patients with schizophrenia do not achieve a satisfactory response with antipsychotic drugs, so various adjunctive medication is used; valproate is one of them. Our results show that a combination of sodium valproate and trifluoperazine is more effective than trifluoperazine alone in the treatment of schizophrenia. This means that sodium valproate can be used as an adjunctive therapy to decrease positive symptom if needed. This finding is consistent with those of Morinigo et al, Afaq et al, Berle et al, Wassef et al and Omranifard et al on the efficacy of valproate as an adjunctive therapy in psychosis. Our finding is not consistent with those of Jacobes et al, Basan et al and Schwartz et al.

### Conclusion

Therefore we can use valproate as an adjunctive drug with antipsychotic in the treatment of schizophrenia especially for positive symptom.

### Limitation of our study

In our study, the number of subjects was low due to rigid inclusion criteria. We are unable to find the exact effective dose of valproate in improving the positive symptom

### Acknowledgment

This study has been conducted by Faculty of Medicine, Yasouj University of Medical Sciences. We appreciate the esteemed authorities of this center, all the employees and students who have assisted us in conducting this study.

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8/2/2013