Add-on Topiramate for the Pharmacological Management of Schizophrenia: A Double Blind Randomized Clinical Trial

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Objective: Glutamate antagonists including anticonvulsant topiramate have been recommended for the pharmacological management of schizophrenia.

Methods: A randomized, double-blind, placebo controlled clinical trial was performed on 32 patients diagnosed with schizophrenia (18-45 years old). Baseline information was gathered on demographic characteristics, vital signs, height, weight, smoking habit, (past) psychiatric history, drug history and adverse effects to medication. Patients were randomly assigned to topiramate group (n=16) or placebo one (n=16). Positive and negative syndrome scale (PANSS) was administered on each patient at baseline, on days 28 and 56.

Results: The mean total PANSS score in topiramate group was 96.87 (85.37-108.37) at baseline, 85.68 (74.67-96.70) on day 28 and 76.87(66.06-87.69) on day 56. These were 101.87 (90.37-113.37), 100.31 (89.29-111.32) and 100.56 (89.74-111.37) respectively in placebo group. General linear model for repeated measure analysis showed that topiramate has lowered PANSS score significantly.

Conclusion: Significant decline was also found in all three PANSS components (negative, positive and psychopathology symptoms). Topiramate can therefore be used as an effective add-on medication in treating schizophrenia.

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Introduction

Although various theories have been proposed about the role of different neurotransmitters in the pathogenesis of schizophrenia, there is not yet any ideal pharmacological treatment available for this chronic mental illness (1).

The relative inefficacy of dopamine antagonists in the management of schizophrenia has prompted many investigators to postulate the involvement of other neurotransmitters in the patho physiology of this disease. In particular, several novel hypotheses have been put forward in the past few years suggesting involvement of excitatory neurotransmitters in the development of psychosis (2,3).

Glutamate, as the major excitatory neurotransmitter in the brain, mediates cortico-cortical, cortico-subcortical and thalamo-cortical transmissions (4). Reduced, unchanged or increased levels of free glutamate have been found in patients with schizophrenia in comparison with patients without schizophrenia. An increased glutamate concentration in the brain tissue would be consistent with a defect in the pre-synaptic release of this amino acid (5). A reduction in glutamate levels would mean a degeneration of glutamatergic nerve terminals (5). The glutamate hyper function has been proposed on the basis of studies of post-mortem brain of patients with schizophrenia and the lack of efficacy of glutamate agonists to treat this condition (4).

Topiramate potentiates GAB Aergic neurotransmission and antagonizes the excitotoxic actions of glutamate at the alpha-amino- 3- hydroxy- 5- methylisoxazole- 4-propionic acid (AMPA)/ kainate (KA) classes of glutamate-gated channels. Therefore, theoretically it can be used in the management

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of schizophrenia (6). Topiramate has been shown to inhibit MK-801-elicited "popping" behavior which seems to be dose-dependent (7).

Few studies have evaluated the efficacy of topiramate on reducing the psychotic symptoms when it is added on already prescribed antipsychotic medication.

To explore the efficacy and tolerability of topiramate, we conducted a randomized, double-blind placebo-controlled clinical trial by adding topiramate to clozapine in the management of treatment resistant schizophrenia.

Materials and Methods

Study was carried out in two psychiatric training hospitals in Isfahan University of medical sciences. Informed written consent was obtained from patients and their family after the local ethics committee of the university approved the study.

A psychiatric interview was performed for each patient to confirm the diagnosis of schizophrenia based on criteria of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) (8). Patients between 18-45 years of age, who were receiving clozpine (dose of ≥100 mg/day) from two weeks prior to start of the research project, were included. Those with another disorder in axis I or axis II, taking mood-stabilizers or other antipsychotic medication, any other chronic medical condition, renal impairment or renal stone and medication-related serious adverse effect were excluded. From 36 patients who had eligibility criteria, four discontinued from the study due to unwillingness or physical ailments.

Baseline information included demographic characteristics, vital signs, height, weight, smoking status, (past) psychiatric history, medication history and medication-related adverse effects. Positive and negative syndrome scale (PANSS) was used for assessing severity of schizophrenic symptoms (9). The scale contains 30 items and assesses positive symptoms (7 items), negative symptoms (7 items) and general psychopathology (16 items).

Using random number generator software, thirty two schizophrenic patients (20 men, 12 women) were randomly assigned to one of two groups. One group (n=16) received clozapine plus topiramate, and the other (n=16), clozapine plus placebo. Topiramate was started with a dose of 25 mg, twice daily, with 25 mg /day increments every 3-4 days to a maximal dose of 300 mg/day, according to patients' symptoms and tolerance.

Whenever necessary, as required (prn) lorazepam was used as adjunctive therapy, with a maximum dosage of 4 mg/day. This was required for 3 and 4 patients in topiramate and placebo groups respectively.

Placebo tablets were made with the same appearance as topiramate tablets in ARYA pharmaceutical company in Iran. The dosage of placebo was also gradually increased in a way similar to increasing the dosage of the topiramate in another group. To comply with blindness, the researcher who allocated the patients randomly to one of two groups had no role in treatment plan or assessment, and the psychiatrist responsible for treatment and completing the PANSS was not informed about patients' medication.

Efficacy was assessed by administering PANSS on days 0 (baseline), 28, and 56. Patients, who were found to have improvement in psychiatric interview, were discharged but were called back for follow-up. Vital signs and adverse effects to medication were checked daily during hospitalization and recorded on baseline, days 28 and 56. Laboratory data included WBC count, Hb, glucose, liver and kidney function tests were measured on baseline and day 56. A trained technician measured the height and weight of the patients to calculate the body mass index (BMI) (weight in kilogram divided by height in meter to the power of two) (10).

The statistical package for the social sciences (version 13.0) was used for the analysis of data (SPSS, Inc, 2004). A P value of 0.05 or less was considered statistically significant for all analyses. T-student test was used to compare age, age at first hospitalization, number of hospitalizations, duration of illness and BMI, and Chi-square

test was used to compare sex and smoking status between treatment and placebo group at baseline. Fisher exact test was used to compare side effects between two groups.

We used a general linear model (GLM) analysis for repeated measure to examine both between- groups and within- groups differences for all time points in PANSS (total scores and components). For each assessment PANSS score was recorded separately and a within-subjects factor is defined in three levels for the three assessment days.

Separate GLM analysis was performed using disease duration and patients' age as co-variate to check their interactive effect on PANSS differences between two groups. Pair wise analysis using T-student test or Mann-Whitney nonparametric test was used for comparison in each time point.

Results

The mean age of the whole sample in both groups was 37.9 (± 5.1) years. The mean duration of illness for patients in both group was 17.9 (± 6.8) years. There was no statistically significant difference between two groups regarding age, sex, age at first (psychiatric) hospitalization, number of (psychiatric) hospitalizations, duration of illness, smoking status and BMI at baseline (Table1). There were no statistically significant differences between two groups in baseline assessment regarding positive symptoms, negative symptoms, general psychopathology and total PANSS scores (Table 2) (Figure 1).

Significant values for repeated assessments (within subject factor; F=7.79, P<0.001) and its interaction with groups (between group factor; F=4.26, P=0.004) were calculated by using the General Linear Model multivariate test. In the between-groups analysis, we found that topiramate-treated patients had lower total PANSS and lower PANSS components compared with placebo group with marginal significances, except for positive symptoms. The GLM analysis shows main between-groups effects (topiramate vs. placebo) for total PANSS (F=3.78; df =1; P=0.061), negative symptoms (F=3.23; df =1; P=0.082), positive symptoms (F=2.73; df =1; P=0.19) and general psychopathology (F=3.89; df =1; P=0.058).

Table 1. Comparison of demographic data and other characteristics in two groups

Specification	Clozapine+Topiramate N=16	Clozapin + Placebo N=16	Pvalue
Age (yr)	37/5 ± 5/7	38.1 ± 4.6	†0.742
Sex (%)	9(56%)	11(68%)	‡0.254
Age at 1st hospitalization	21.41 ± 4.84	20.72 ± 7.68	†0.757
Number of hospitalization	9.72 ± 5.81	7.14 ± 5.31	†0.229
Duration of illness	17/7 ± 7/8	18.1 ± 5.4	†0.855
Smoking status	12 (75%)	10(62%)	‡0.353
BMI (Kg/m ^{2})	24.12 ± 3.35	25.21 ± 4.42	†0.652

† T-student (mean ± SD)
‡ ^{2} test

Table 2 . Analysis of PANSS score changes on days 28 and 56 in Topiramate and Placebo groups

	Clozapine + Topiramate	Clozapine + Placebo	t	P value
Positive symptoms				
Baseline	24.6 ± 6.19	23.50 ± 7.84	0.22	0.82
Changes after 28 days	-3.06 ± 3.56	-0.75 ± 3.82	-1.76	†0.087
Changes after 56 days	-5.68 ± 4.36	-0.56 ± 4.41	-3.30	0.002
Negative symptoms				
Baseline	24.75 ± 8.53	27.68 ± 10.13	-0.88	0.38
Changes after 28 days	-3.31 ± 3.23	-1.00 ± 1.63	-2.55	†0.018
Changes after 56 days	-5.87 ± 3.73	0.00 ± 4.60	-3.96	<0.001
General psychopatholgy				
Baseline	48.06 ± 12.01	50.68 ± 10.74	-0.65	0.52
Changes after 28 days	-4.81 ± 6.49	0.18 ± 5.78	-2.30	†0.029
Changes after 56 days	-8.43 ± 7.99	-0.75 ± 7.49	-2.80	†0.009
Total PANSS				
Baseline	96.87 ± 21.98	101.87 ± 23.05	-0.62	0.53
Changes after 28 days	-11.18 ± 8.72	-1.56 ± 9.23	-3.03	0.005
Changes after 56 days	-20.00 ± 11.96	-1.31 ± 11.13	-4.57	<0.001

† According to Shapiro-Wilk test, normality assumptions were violated, but Mann-Withney test had the same results.

In topiramate-treated subjects, BMI was 24.12 (± 3.35), 23.61 (± 3.75) and 23.21 (± 3.54) on baseline, day 28 and 56 respectively. In the other group, BMI was 25.21 (±4.42), 25.37 (±4.68) and 25.42 (±4.75) on baseline, day 28 and 56, respectively. None of these figures in neither groups show any significant changes.

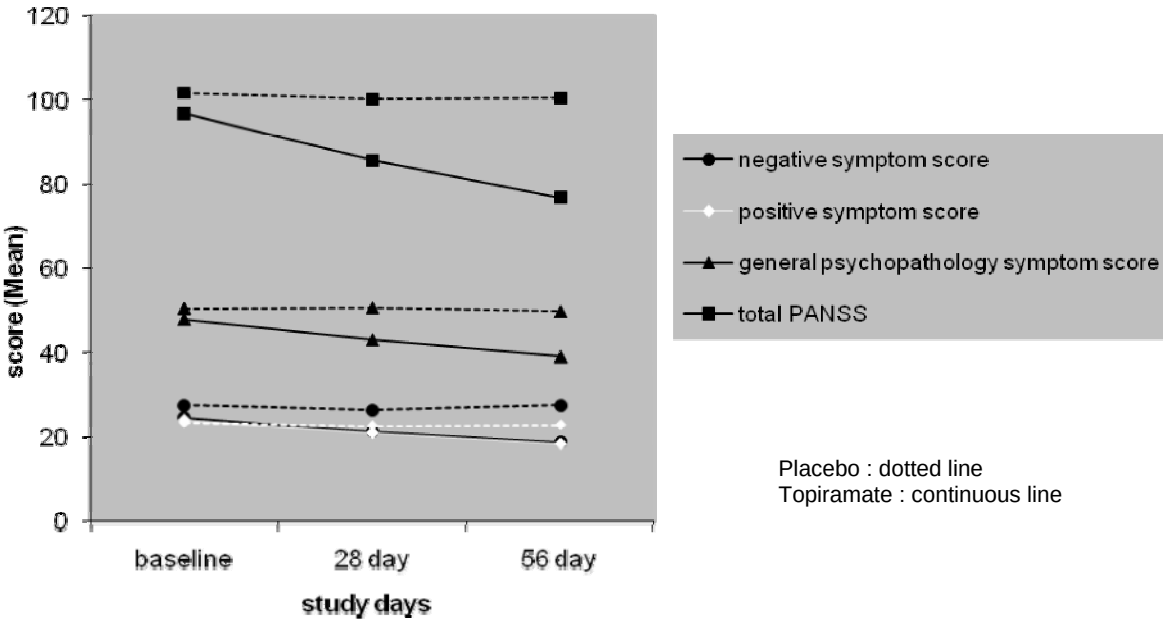
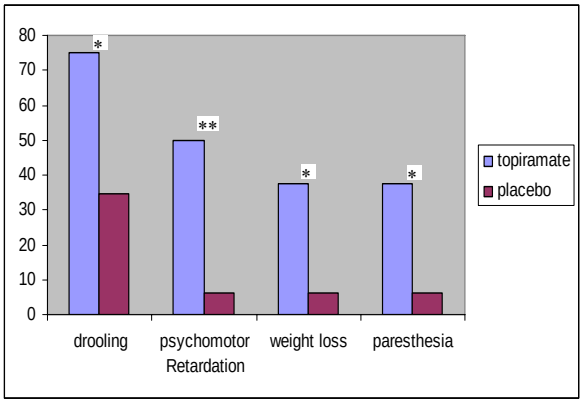


Figure 1 . PANSS scores on baseline, days 28 and 56 in Topiramate and Placebo groups

Some of the patients in topiramate group developed side effects such as psychomotor retardation, weight loss, drooling and paraesthesia on day 56. When compared to placebo group, this appeared statistically significant (Figure 2). Other adverse effects such as tremor, lack of appetite, constipation, dizziness, urinary incontinence, sedation and weight gain were reported in both groups without any statistically significant differences between them.



* P≤ 0.05
** P≤ 0.01

Figure 2. Adverse effects differences between two groups

Data on laboratory investigation and vital signs measurements revealed non-significant differences in two groups at the beginning and the end of the study. There was no report of serious adverse events resulting in discontinuation of medication in neither group.

Discussion

Our study shows significant differences in the PANSS mean scores (positive symptoms, negative symptoms and general psychopathology) between the two groups after an 8-week follow-up period. It also shows that the improvement in general psychopathology score in the topiramate group during follow-up period was observed earlier in comparison to the other components of PANSS.

In an add-on design study of 24-week duration, Dursun and Deakin studied the efficacy of topiramate (with a maximum dosage of 300 mg/day) on patients with resistant schizophrenia. They reported a significant improvement in positive and negative symptoms (11). In another study (case-series on 5 patients), topiramate was used with an initial dosage of 50 mg/day and

a maximum dosage of 200-300 mg/day. The results showed that there was a significant improvement in positive and negative symptoms (12). Tiihonen *et al.* performed a clinical trial adding 300mg/day topiramate to the ongoing treatment of schizophrenic patients, in which general psychopathology scores showed significant improvement (13). Our study also shows a significant improvement in positive and negative symptoms in topiramate group in 8th-week, and in general psychopathology score in 4th-week.

In a case-study by drapalski et al in 2001 on a patient with schizophrenia, topiramate was shown to attenuate the severity of negative symptoms (5). In our study, there was improvement in negative symptoms as well as positive symptoms.

In an animal study, addition of topiramate to rats treated with raclopride increased dopamine in the medial prefrontal cortex. This observation supports the use of topiramate as an adjunct therapy in reducing negative symptoms (14). Basic studies on glutamate receptors (NMDA, AMPA and KA) have shown similarity of symptoms induced by phencyclidine (PCP) and ketmine with positive and negative symptoms of schizophrenia and impaired tasks performance associated with frontal lobe dysfunction (15,16). Besides, results of post mortem studies on the brain of patients with schizophrenia show increased binding of [3H]- kainate and D-[3H]- aspartate in the frontal cortex, decreased non-NMDA receptor mRNA in the cortex, and increased binding of [3H]-MK801 in the putamen (17). Additionally, abnormalities in glutamate receptor density and function in the brain of schizophrenic patients have been found (18). All these evidence support the hypothesis of glutamate model in the pathogenesis of schizophrenia (i.e. inhibition of glutamate receptors in the nucleus accumbens and prefrontal cortex may increase positive and negative symptoms, respectively) (19-20).

Regarding the side effects, our study shows that paresthesia, psychomotor retardation and weight loss are significantly higher in topiramate group. Moreover, we found out that topiramate exacerbated the clozapine-induced drooling in our patients.

In a study performed by Ko *et al*, it was shown that topiramate-induced weight loss was dose related (lesser weight loss was observed in 100mg compared to 200 mg per day dosage) (21). In our study weight loss was significantly observed in topiramate group (figure 2). The exact mechanism by which topiramate causes weight loss is not known yet. However, there are postulations that topiramate may enhance GABA receptor activity or modulate glutamate activity at AMPA receptor. The modulation of lipoprotein lipase activity has been proposed as well (22-24). Zheng *et al* also showed that injecting AMPA receptor antagonists inhibits eating and drinking in rats in a dose-dependent manner (25). Other side effects of topiramate include paresthesia, psychomotor retardation and drooling.

The limitations of our study are small number of patients in each group and a short follow-up duration.

The result of our study recommnds the use of topiramate as an adjunctive therapy, especially in the management of treatment resistant schizophrenia. Glutamate antagonists such as topiramate can be effective in controlling not only positive and negative symptoms of schizophrenia but also antipsychotic-induced weight gain.

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