Original Article

Effect of Topiramate Augmentation in Chronic Schizophrenia: A Placebo-Controlled Trial

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Abstract

Background: The limitations of antipsychotics for treatment of schizophrenia have led to investigation of the usefulness of pharmacological augmentation strategies. Clinical studies have provided evidence for glutamate abnormalities in schizophrenia. Topiramate is an anticonvulsant drug with alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor antagonist properties; therefore, the objective of the present study was to explore the therapeutic efficacy of topiramate as an adjunctive medication in schizophrenia.

Methods: A 17 week, double-blind, placebo-controlled clinical trial was performed on 80 patients (25 – 65 years) from 2005 – 2007. All were hospitalized in Mashhad psychiatric hospitals with chronic DSM-IV-TR-diagnosed schizophrenia. All participants received up to 300 mg/day of clozapine. In addition, participants randomly received either topiramate (200 – 300 mg/day) or placebo gradually added to their ongoing treatment. Efficacy of medication was measured by administering

Positive and Negative Syndrome Scale at baseline and weeks 4, 8, 12, and 17.

Results: During the study, 5 patients from the placebo group and 12 participants from topiramate group were excluded. Clozapine and topiramate group showed significant decreases in all three subscales of PANSS values from baseline, with the maximum efficacy in week 12. However, after tapering topiramate, the general psychopathology sign was the only subscale that showed a significant difference. The clozapine and placebo group showed a significant decrease in all three subscales of PANSS values compared to baseline. The significant efficacy for all subscales was obtained at the end point. No significant differences in PANSS scores from baseline to end point were noted between case and control groups.

Conclusion: Augmentation of clozapine and topiramate did not significantly decline patterns in any of the three subscales of PANSS compared to the clozapine and placebo group. Irct ID: IRCT138904014236N1

Keywords: chronic schizophrenia, placebo-controlled trial, topiramate

Introduction

Schizophrenia is a chronic disorder of profoundly disruptive psychopathology that involves different aspects of behavior. The effect of the illness is always severe and is usually long-lasting. In the United States, the lifetime prevalence of schizophrenia is about 1%.[1] Although different antipsychotic medications are available for the treatment of schizophrenia, approximately 60% of patients who receive medication will improve to some extent and others demonstrate variable levels of resistance to the medications.[2] The limitations of antipsychotics for treatment of schizophrenia have led to the investigation of the usefulness of pharmacological augmentation strategies for these components.

The involvement of glutamate transmission in schizophrenia has been under investigation since 1989. Hyper-function of glutamatergic pathways in the frontal cortex of schizophrenic patients was first proposed by Deakin et al.[3] Recent clinical studies have provided more evidence for glutamate abnormalities in schizophrenia. Some of this information comes from different studies examining the antiepileptic medication lamotrigine.[4] Lamotrigine's anticonvulsant action has been attributed to the increase in γ-aminobutyric acid (GABA) release and also antagonism of voltage-gated sodium channels leading to a reduction in glutamate release.[5–7]

There is also a glutamatergic hypo-function hypothesis of schizophrenia based on the ability of the non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, phencyclidine (PCP), to induce psycho-mimetic effects in healthy human volunteers indistinguishable from schizophrenia. PCP mimics the positive and negative symptoms and cognitive dysfunction as well as formal thought disorders and even auditory hallucinations. It could exacerbate psychosis in schizophrenic patients.[8,9] The two opposing glutamatergic hypo-function and hyper-function theories have been reconciled by the fact that PCP has a glutamate release increasing potential beside its NMDA associated channels blocking properties.[10] Therefore, the psychotic symptoms of PCP could be due to glutamate release potentiation and not due to the reduction of glutamate activity.[6]

Topiramate is an anticonvulsant drug with alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor antagonist properties and a GABA potentiating action.[8,9] Because of these properties, topiramate could be chosen as a novel medication to address downstream consequences of NMDA receptor hypo-function, which are potentiation of GABAergic neurotransmission and antagonism of the excitotoxic actions of glutamate at the alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) classes of glutamate-gated channels.[9,11,12]

Clinical results suggest that treatment with topiramate may improve negative symptoms and cognitive dysfunction in schizophre-

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nia when added to a stable dose of antipsychotic medication;[8,13–15] although much of this information is based on open-label studies, case reports and case series.[16] Therefore, the objective of the present study was to explore the therapeutic efficacy of topiramate as a potential adjunctive medication in schizophrenia.

Materials and Methods

This study was a 17 week, double-blind, placebo-controlled comparison of placebo and topiramate as an adjunct treatment for subjects diagnosed with chronic schizophrenia performed from October 2005 to October 2007. A total of 292 patients who had chronically been hospitalized in Ibn-e-Sina and Hejazi Psychiatric Centers of Mashhad University of Medical Sciences were screened. All were continuously hospitalized for at least six months in chronic wards; in addition, their symptoms were resistant to at least two different antipsychotic therapy trials other than clozapine. Among them, 80 subjects aged 25 to 65 with the diagnosis of chronic schizophrenia based on Diagnostic and Statistical Manual of Mental Disorders 4th edition-Text Revision (DSM-IV-TR) who met the inclusion criteria and agreed to participate in the trial were enrolled. Direct interviews with the subjects and their families were conducted by two psychiatrists and responses were combined to ascertain diagnoses. The psychiatrist making the clinical diagnosis was board-certified. Baseline information including vital signs, weight, height, demographic characteristics, medication history and medication-related adverse effects was collected. All patients were examined to rule out neurological deficits or other medical conditions, substance use disorder (other than nicotine), history of intolerance to topiramate, ongoing treatment with any antiepileptic drug or any antipsychotic agent other than clozapine within four weeks.

After meeting all inclusion and exclusion criteria, subjects were randomly assigned to receive topiramate or placebo in combination with their stable dose of clozapine. Randomization was appointed according to a computer-generated randomization schedule that was prepared before the study. Written informed consent (accordance declaration of Helsinki) was obtained from patients or their legal guardians. Medication was prescribed in a double-blind manner. The raters and clinicians who prescribed topiramate or placebo and adjusted the dose based on response or tolerability were different. All raters (trained psychologists supervised by psychiatrists) who performed efficacy and tolerability rating scales were blinded to the subjects' assigned groups. Optimum dosage of clozapine was continued for all participants for four weeks and then topiramate or placebo (identical shape and color as topiramate) was gradually added to their ongoing treatment. Topiramate was prescribed at a dose of 50 mg on day 0. Every two days, the dose was increased by 50 mg/day, based on tolerability. The maximum dose allowed was 150 mg twice a day. Subjects were maintained on topiramate or placebo for eight weeks, thereafter they were tapered and discontinued gradually in one week. They were followed for an additional four weeks on their stable antipsychotic medications.

Two psychiatrists unblinded to the treatment status of the patients who did not perform efficacy and tolerability rating scales were assigned to monitor for the presence of psychiatric symptoms and the development of adverse effects related to topiramate.

Efficacy of medication as primary outcome variable was measured by administering the Positive and Negative Syndrome Scale (PANSS). PANSS assessments (95% confidence interval) were performed at baseline and on weeks 4, 8, 12, and 17 in both groups. The PANSS provides a comprehensive measure of symptomatology. It consists of 18 items from the Brief Psychiatric Rating Scale, measuring positive symptoms, general psychopathology, and affective symptoms and 12 items from the psychopathology rating schedule. Together these form 7 items to measure positive symptoms, 7 items to measure negative symptoms and 16 items to measure general psychopathology. The PANSS items are frequently summed to provide a general index of symptom severity.[17–19]

Statistical analysis

Collected data were analyzed by appropriate descriptive and analytic statistical tests including *t*-test and Chi-square to compare demographic and baseline variables, independent sample *t*-test for between two group comparisons and paired-samples *t*-test for within-group comparisons. Statistical Package for the Social Sciences (SPSS) version 14 was used. Reported differences were significant at the 0.05 level or less.

Results

A total of 80 subjects were enrolled with all receiving clozapine up to 300 mg daily. Forty subjects were randomly assigned to the topiramate group (200 – 300 mg/day) and forty to the placebo group. During the study, five patients were removed from the placebo group because they needed other medications. In the topiramate group, 12 participants were excluded because of side effects and exacerbation of positive symptoms. In the topiramate group, 16 patients received 200 mg/day and 12 subjects received 300 mg/day of topiramate (Figure 1).

The two groups had no significant differences in age and gender (P=0.46 and P=0.43, respectively). Comparison analysis showed no significant differences in any of the three subscales of PANSS (negative, positive, and psychopathology signs) between the two groups at baseline (P=0.06, P=0.49 and P=0.47, respectively; Table 1).

The clozapine$_{plus}$topiramate group showed significant reduction in all three subscales of PANSS values from baseline to week 12; with the maximum change observed at week 12. Following the taper of topiramate at week 17, the psychopathology subscale was the only one to maintain statistical significance (Table 2).

The clozapine$_{plus}$placebo group showed significant reduction in all three subscales of PANSS values compared to the baseline with the maximal changed noted for all subscales at week 17 (Table 2).

There were no statistically significant differences in PANSS score differences on any of the three subscales from baseline to endpoint between the clozapine and topiramate group compared to the clozapine and placebo group. Topiramate was not superior to placebo (Table 3). Although at week eight, there were specific differences in the negative and general subscale between both groups. In the placebo group, the mean changes from baseline to eight weeks were superior to topiramate.

Adverse effects in both groups are listed in Table 4, of which no specific differences are noted between them.

Discussion

According to our clinical observation, we did not prove the suggested synergistic effect of clozapine and topiramate. Thus, clo-

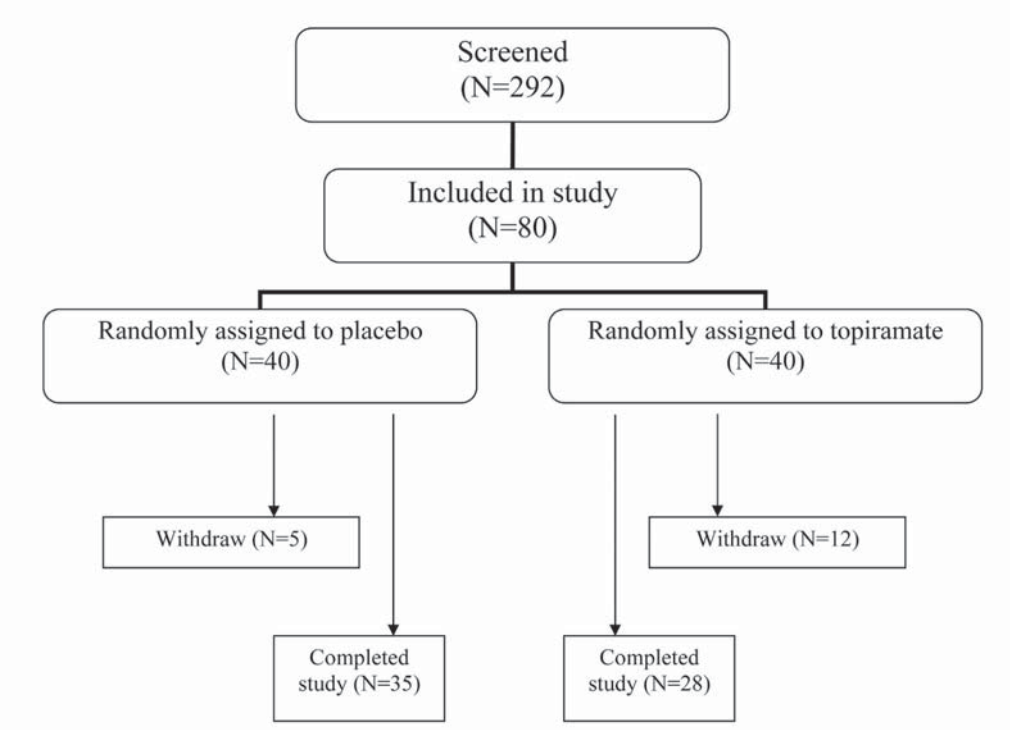

Figure 1. Disposition of study subjects.

Table 1. Basic demographic and clinical characteristics of subjects.

Characteristics	Topiramate (40)		Placebo (40)		Statistical analysis
	N	(%)	N	(%)	*P*-value
Sex					
Male	37	(92.5)	31	(77.5)	*P*=0.07
Female	3	(7.5)	9	(22.5)	
	Mean PANSS score	(SD)	Mean PANSS score	(SD)	
Age	45.12	(9.82)	46.93	(9.83)	*P*=0.46
Baseline PANSS sub-scale					
Negative	21.81	(5.25)	24.50	(5.84)	*P*=0.06
Positive	14.25	(1.77)	13.94	(1.90)	*P*=0.49
General psychopathology	32.28	(4.71)	31.27	(6.51)	*P*=0.47

Table 2. Outcome measure of subjects.

Baseline PANSS sub-scale	Topiramate							Placebo						
	Baseline score	Adjusted mean change in score from baseline (week 8)	Statistical analysis	Adjusted mean change in score from baseline (on week 12)	Statistical analysis	Adjusted mean change in score from baseline (on week 17)	Statistical analysis	Baseline score	Adjusted mean change in score from baseline (week 8)	Statistical analysis	Adjusted mean change in score from baseline (week 12)	Statistical analysis	Adjusted mean change in score from baseline (week 17)	Statistical analysis
	Mean (SD)	Mean (SD)	*P*-value	Mean (SD)	*P*-value	Mean (SD)	*P*-value	Mean (SD)	Mean (SD)	*P*-value	Mean (SD)	*P*-value	Mean (SD)	*P*-value
Negative	21.81 (5.25)	0.94 (4.52)	0.93	3.84 (5.06)	0.00	0.59 (5.89)	0.21	24.50 (5.84)	1.88 (4.30)	0.01	1.88 (5.60)	0.00	2.03 (5.46)	0.04
Positive	14.25 (1.77)	0.06 (2.43)	0.83	1.37 (3.25)	0.00	0.77 (3.19)	0.11	13.94 (1.90)	0.22 (2.47)	0.77	0.55 (2.40)	0.08	0.93 (2.86)	0.01
General psychopathology	32.28 (4.71)	0.87 (3.68)	0.10	8.12 (5.42)	0.00	8.68 (6.60)	0.00	31.27 (6.51)	5.33 (6.88)	0.00	8.71 (8.46)	0.00	7.22 (7.90)	0.00

Table 3. Outcome measure of subjects.

Baseline PANSS sub-scale	Baseline score		Adjusted mean change in score on week 8 from baseline		Statistical analysis	Adjusted mean change in score on week 12 from baseline		Statistical analysis	Adjusted mean change in score on week 17 from baseline		Statistical analysis
	Topiramate	Placebo	Topiramate	Placebo		Topiramate	Placebo		Topiramate	Placebo	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	*P*-value	Mean (SD)	Mean (SD)	*P*-value	Mean (SD)	Mean (SD)	*P*-value
Negative	21.81 (5.25)	24.50 (5.84)	0.94 (4.52)	1.88 (4.30)	0.05	3.84 (5.06)	1.88 (5.60)	0.57	0.59 (5.89)	2.03 (5.46)	0.62
Positive	14.25 (1.77)	13.94 (1.90)	0.06 (2.43)	0.22 (2.47)	0.96	1.37 (3.25)	0.55 (2.40)	0.17	0.77 (3.19)	0.93 (2.86)	0.66
General psychopathology	32.28 (4.71)	31.27 (6.51)	0.87 (3.68)	5.33 (6.88)	0.00	8.12 (5.42)	8.71 (8.46)	0.74	8.68 (6.60)	7.22 (7.90)	0.16

Table 4. Adverse events reported for subjects.

Adverse events	Topiramate (40)		Placebo (40)	
	N	(%)	N	(%)
Paresthesis	0	(0%)	0	(0%)
Dizziness	1	(2.5%)	0	(0%)
Drowsiness	0	(0%)	0	(0%)
Ataxia	1	(2.5%)	0	(0%)
Diplopia	1	(2.5%)	0	(0%)
Tremor	2	(5%)	0	(0%)
Speech-related problem	0	(0%)	0	(0%)
Blurred vision	0	(0%)	0	(0%)
Muscle weakness	0	(0%)	0	(0%)
Headache	0	(0%)	0	(0%)
Hair loss	0	(0%)	0	(0%)
Weight loss	6	(15%)	0	(0%)
Constipation	2	(5%)	0	(0%)
Nausea	0	(0%)	1	(2.5%)
Psychosis exacerbation	2	(5%)	0	(0%)

zapine combined with topiramate is not an effective augmentation in the treatment of schizophrenia disorder. This finding is consistent with other findings.[20] In 2001, Dursun and Deakin proposed that glutamate hyper-function in schizophrenia has a pre-synaptic basis as lamotrigine, a glutamate excess release inhibitor, and not topiramate, a glutamate kainate/AMPA receptor antagonist, which augmented clozapine treatment of schizophrenic patients.[6] In 2002, Millson et al. in a case series treated three men and two women with chronic schizophrenia adding topiramate to their current medication. They noted a deterioration of both positive and negative symptoms in all subjects a month after the maximum dose was administered.[21] Another interesting research suggested that adjunctive topiramate facilitates the NMDA-induced currents when added to the selective dopamine D2/3 antagonist, raclopride, and enhances its antipsychotic-like effect through involvement of dopamine and D1 receptors, whereas neither raclopride nor topiramate had any effect when given alone. Previous data had shown that atypical (i.e., clozapine), but not typical, antipsychotic drugs facilitate NMDA-induced currents including a mechanism dependent on dopamine and D1 receptor activation. On the other hand, the combination of raclopride and topiramate act similarly to clozapine, and topiramate is no longer able to facilitate clozapine's effect on NMDA-induced currents.[8] These findings support our results.

There is, however, the possibility that glutamate may exert a psychotogenic effect at a postsynaptic site, which remains unidentified. Nevertheless, Dursun et al. (2001) showed reduced glutamate release induced by lamotrigine and blockade of non-NMDA receptors with topiramate have antipsychotic effects.[6] In 2003 Deutsch et al. reported that administration of topiramate (average dose, 110.42 mg/day) decreased total scores on the PANSS.[12] According to our results, in the clozapine and topiramate group scores in all subscales of PANSS decreased before topiramate was discontinued. When topiramate was tapered, PANSS scores gradually increased; which was similar to the previous report, although there was not any significant difference in PANSS scores between the

topiramate and placebo groups at the end of the study. Drapalski et al. suggested an improvement in negative symptoms in a patient with schizophrenia when 350 mg/day of topiramate was added to a stable regimen of antipsychotic medication.[14] Study by Eltayb et al. in 2005, showed similar results.[22] In 2008, Afshar et al. found the same results and reported that topiramate can be an effective medication especially in controlling negative symptoms.[13] Our study could not show the same results and the differences among the dosages administered in different studies does not seem to be the main reason because the effective dose varies between 110 to 350 mg/day in different reports. In 2005, Tiihonen et al. found that topiramate was more effective than placebo in reducing PANSS and general psychopathologic symptoms, whereas no significant improvement was observed in positive or negative symptoms.[23] In 2007, Migliardi et al. had the same findings and suggested topiramate as an effective adjuvant treatment in reducing general psychopathologic symptoms in patients with schizophrenia resistant to treatment with second-generation anti-psychotics.[24] In our research the decrease in general psychopathologic symptoms scores in the clozapine and topiramate group remained significant in comparison to baseline scores even after topiramate was tapered. However, it is important to distinguish between clinical meaningful changes in patients and significant declines in rating scores seen in some studies.[25]

Our findings also proposed that patients who received clozapine in the clozapine and placebo regimen group had significant lower PANSS scores, especially the positive subscale at the end of the study (week 17) in comparison to scores obtained in weeks 0, 8, and 12. As the use of the PANSS assists in the definition of "response," it is obvious that although serotonin-dopamine antagonists usually require 4 to 8 weeks to reach full effectiveness,[2] it may take more than 12 weeks for the full clinical effects of clozapine to become apparent. In the literature, it is emphasized that clinical improvement may take six months of treatment with clozapine in some particular treatment-refractory persons,[1,2] so improvement in PANSS sub-scales in our study could be considered a clozapine therapeutic effect. In placebo-controlled trials of short duration (<6 – 8 weeks), especially in probands with schizophrenic disorder who have more severe pathology, they are less vulnerable to substantial placebo response.[26] Our study involved chronic schizophrenic patients with 17 weeks duration of medication thus, the placebo response could not be responsible for the absolute changes in PANSS sub-scale scores.

There are some differences between other studies and ours. One, the subjects of our sample were in-patient chronic participants; thus there were more medication-resistant patients in our sample. An increase in PANSS score after week 12 could be considered as probable evidence. In addition, confounding variables such as different familial atmosphere or expressed emotions, various diets, different medications or incomplete adherence, environmental facilities or social relationships did not affect our research because all participants were inpatients during the study.

Our findings indicate that at the dosages recommended in this study, topiramate is not well tolerated in all participants (Table 4). In the topiramate group, 12 patients (30%) had side effects and exacerbation of positive symptoms. Some studies have shown that topiramate is well tolerated by patients at the same dosages and even may promote long-term adherence to treatment by inducing body weight loss.[16,24,27–29] There are different reports on topiramate side effects such as sleepiness, ataxia, and psychomotor slowness and it may also exacerbate, worsen, or even induce psychosis.[12,21,30–34]

Reduced concomitant medication usage could lead to improved patient compliance with treatment via reduction in potential drug interactions.[35] Although some authors believe that topiramate can raise patient compliance with treatment by reversing the weight gain associated with antipsychotic administration, the results should be interpreted conservatively. Clinicians need to be aware of adverse psychiatric events in patients taking topiramate and consider decreasing the dose or discontinuing the medication altogether.

The pharmacological mechanisms of topiramate augmentation for psychotic patients are still elusive and controversial. There is a need for further preclinical and clinical research using pharmacological agents such as pre- and postsynaptic glutamate receptor agonists and antagonists to explore the intriguing role of glutamate neurotransmission in schizophrenia, so that the useful augmentations for clozapine treatment and probable therapeutic action of topiramate would be elucidated.

The main finding of this study is that the augmentation of clozapine and topiramate did not significantly decline patterns in any of three subscales of the PANSS compared to the clozapine and placebo group.

Limitations

This study lacked laboratory equipment to check serum levels of clozapine, therefore clinicians adjusted the dosage of clozapine clinically. This was the main limitation of our study.

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