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Topiramate Augmentation in Resistant OCD: *A Double-Blind Placebo-Controlled Clinical Trial*

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ABSTRACT

Objectives: Glutaminergic dysfunction has been shown to be related to the pathphysiology of obsessive-compulsive disorder (OCD). Topiramate is an antiepileptic that inhibits glutaminergic action. The aim of this study is to evaluate the efficacy of topiramate augmentation in patients with treatment resistant OCD.

Methods: This augmentation trial was designed as a 12-week randomized, placebo-controlled, double-blind study. Forty-nine patients suffering from OCD who had failed to respond to at least 12 weeks of treatment of an adequate and stable dose of a selective serotonin reuptake inhibitor (SSRI) were randomly allocated to receive topiramate or placebo plus their current anti OCD treatment. Yale-Brown Obsessive Compulsive Scale (Y-BOCS) was the primary outcome measure. Treatment response was defined as 25 % or more decrease in scores of Y-BOCS. The mean dosage of topiramate was 180.15 mg/day (range 100–200 mg/day).

Results: Forty-one patients (20 of 24 in topiramate group; 21 of 25 in placebo group) completed the trial. The topiramate group showed significant improvement over the study period (mean Y-BOCS score at week 12 as compared with baseline: P=.000). Those receiving topiramate experienced a mean decrease of 32.0% in Y-BOCS score, compared with 2.4% decrease for those receiving placebo. Twelve patients in the topiramate group versus no patient in the placebo group were rated as responder.

Conclusion: The results of our study demonstrated that topiramate may augment the

FOCUS POINTS

- Glutaminergic dysfunction is related to the pathophysiology of OCD.
- Topiramate inhibits glutaminergic action.
- Topiramate augmented the effects of SSRIs in OCD resistant patients.
- The augmenting effect may be due to glutamate modulating role.

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therapeutic effect of SSRIs in treatment-resistant OCD patients. However, it should be noted that our study is preliminary and larger double-blind studies are needed to confirm these results.

INTRODUCTION

Obsessive–compulsive disorder (OCD) is a chronic debilitating disorder with a lifetime prevalence of 2% to 3%.[1,2] Currently, selective serotonin reuptake inhibitors (SSRIs) are considered to be the first choice agents for the pharmacologic treatment of OCD.[3] However, up to 50% of patients with OCD have failed to respond in SSRI trials.[4]

The limited effectiveness of SSRIs suggests the critical involvement of other neurotransmitter systems. Evidence for the involvement of the glutamatergic system in OCD is steadily mounting.[5]

Evidence from Neuroimaging and Glutamate Concentration Studies

Several studies have shown that patients with OCD have higher cerebrospinal fluid (CSF) glutamate levels than normal individuals.[6,7] In this line, the established relationship between the metabolic rate of neurons and glutamatergic transmission[8,9] suggests the existence of glutamatergic hyperactivity in OCD, which was indicated by the glucose metabolic rate changes reported in positron emission tomography studies.[10,11] The implication of abnormalities in the glutamatergic system in OCD is also supported by neuroimaging studies using spectroscopy that allow to measure glutamatergic concentrations.[12] Glutamatergic concentrations have been found greater in the orbitofrontal cortex[13] and the striatum,[14] but smaller in the anterior cingulate cortex,[15] suggesting that these brain regions may play important roles in OCD. Finally, Rosenberg and colleagues[14] have shown that glutamatergic concentrations within the caudate nucleus decreased to levels comparable with those of control subjects after 12 weeks of SSRIs treatment, in parallel with OCD symptom severity. Therefore, the anti-obsessive-compulsive effects of SSRIs may be related to their ability to modulate glutamatergic concentrations.

Evidence from Genetic Studies

In 2004, Arnold and colleagues[16] provided the first report of a positive association between a glutamatergic system gene (GRIN2B) and OCD. In addition, polymorphisms in the glutamate transporter gene (SLC1A1) have been reported to be associated with OCD in several studies.[17-19] Studies of genetic of early onset OCD also have shown that glutamate transporter gene SLC1A1 on 9p24 is related to pathphysiology of OCD.[20] Indeed the most reliable evidence for gene association in OCD exists for the glutamate transporter gene SLC1A1, which together with recent reports of association for other genes directly involved in glutamatergic signaling at synapses has provoked a shift in attention to glutamatergic neurotransmission as a target for OCD pharmacotherapy.[5]

Evidence from Glutamatergic Neurotransmission-modulating Agents in the Treatment of OCD

Numerous glutamatergic modulating agents are currently being tested in the treatment of OCD. Riluzole is suspected to reduce glutamate release in the brain via multiple presynaptic mechanisms.[21] The results of several trials with riluzole have been remarkably consistent, with roughly half of the patients treated thus far experiencing significant treatment response.[22-24] Memantine, an uncompetitive NMDA receptor antagonist has exhibited positive effects in treatment-resistant OCD.[25,26] In this line, Stewart and colleagues[27] in a case controlled study found memantine to be superior to placebo as an augmenting agent in severe OCD. Amantadine is structurally and functionally related to memantine and has recently been shown to inhibit marble burying in mice.[28] Consistent with glutamatergic interventions, glycine, an NMDA glutamate receptor agonist, has approached efficacy in treatment of OCD in several studies.[29,30] Overall, Bhattacharyya and colleagues[31] concluded that glutamatergic dysfunction is the newer target for anti-obsession drugs.

Topiramate is a novel antiepileptic effective against both partial and generalized seizures.[32] It has also shown to have some positive psychotropic properties.[33,34] Topiramate directly inhibits glutamate action via the Amino-3-Hydroxy-5-Methyl-4-Isoxazole Propanoic Acid 9 (AMPA)/kainate subtype of glutamate receptors. It also enhances the activity of γ-aminobutyric acid ($GABA_A$) at nonbenzodiazepine sites.[35]

In view of glutamate dysfunction postulated in OCD and topiramate's effect at the glutamate receptor, we conducted the first double-blind placebo

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controlled trial to examine the efficacy of topiramate augmentation in treatment resistant OCD patients.

METHODS

The trial was designed as a randomized, placebo-controlled, double-blind study. Patients were diagnosed according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria for OCD by a board certified psychiatrist through Structured Clinical Interview for *DSM-IV*, Clinical Version (SCID-I). Exclusion criteria were any other axis I and II diagnosis, major medical problems (cardiovascular, pulmonary, renal or gastrointestinal diseases), pregnancy and substance or alcohol abuse. All the patients provided informed consent and the study was approved by the ethic committee of Bushehr University of Medical Sciences that adheres to the Declaration of Helsinki Ethical Principles for Medical Research involving human subjects.

The patients were recruited from Abolfazl Psychiatric Clinic affiliated by Bushehr University of Medical Sciences from July 2008 to July 2009. The patients had failed to respond to at least 12 weeks of treatment of an adequate and stable dose of a SSRI (fluoxetine, citalopram or serteraline), as reflected by a baseline Yale-Brown Obsessive Compulsive Scale (Y-BOCS) of 18 or greater. Mean Y-BOCS baseline score was "27.4". Subjects had failed an average of 2.4 (SD, 1.8) SSRI trials judged to be of adequate dose and duration. The concurrent medications at baseline were fluoxetine (n=24, mean dosage=53.6 (40–80 mg/day); citalopram (n =14, mean dosage 49.9 mg/day (40–80 mg/day) and serteraline (n=11, mean dosage=256.5 mg/day (200–350 mg/day).

The patients were placed in one of the two treatment groups randomly: placebo or topiramate. We used a standard randomization procedure generated by computer to have random sample set. The placebo and topiramate tablets had the same shape and color. The placebo tablets were prepared by Bushehr university pharmacology unit. The patients and the examiner were blind about the consuming medication as the same number of similar pills was provided. The ratings were done by the examiner who was a trained psychologist and unaware of adverse events.

Treatment duration was 12 weeks. Topiramate was added to the subject's OCD regimen initially at 25 mg/day, increased in 25-mg increments weekly to a target dose of 200 mg/day. No dose escalation was administered for patients that could not tolerate higher doses. The mean dosage of topiramate was 180.15 mg/day (range 100–200 mg/day). Subjects were interviewed at screening, baseline, and biweekly till the end of the study. Safety and tolerability were assessed using spontaneously reported adverse event data and rates of premature termination for side effects. During the study psychological interventions were not allowed. All patients completed a general medical examination and blood chemistry tests, including TSH, FT4, liver function test, renal function test and complete blood count before the study.

The primary efficacy measure was Y-BOCS.[36] The Y-BOCS and Hamilton Rating Scale for Depression, 17-item ($HAM\text{-}D_{17}$)[37] were administered before starting the treatment and at the end of week 12. The efficacy index of Clinical Global Improvement was employed at the end of the study. Topiramate and placebo were prepared with the financial support of Bushehr University.

Statistical Analysis

Treatment response was defined as $\geq$25% decrease in the scores of Y–BOCS. We compared the demographic and clinical characteristics of the groups at baseline using X2 and Mann-Whitney U tests. Mann-Whitney U test was used to compare the 2 groups for significantly different effects, and the Wilcoxon signed ranks test computed the differences within groups. Response rates were compared between the groups at the endpoint. The analysis was performed only on completers. The data are presented with mean (SD). All *P* values were two-tailed, and statistical significance was set at the 5% level. Statistical assessments were performed by SPSS for Windows version 12.0.

RESULTS

Forty one patients (20 of 24 in topiramate group and 21 of 25 in placebo group) completed the trial. The drop outs occurred any time during the study. In the topiramate group, the patients' withdrawals were due to adverse events [gastrointestinal disturbance (n=2), headache (n=1) and memory problems (n=1)]. In the placebo group, four patients dropped from the study due to loss of efficacy (n=2) and adverse events (headache [n=1] and gastrointestinal disturbances [n=1]).

The mean age of the patients was 34.9 years; 57.1% of the participants were female. Demographic and baseline clinical characteristics are shown in Table 1. There was no significant difference between the two groups regarding

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demographic and baseline clinical characteristics. All patients had both obsessive and compulsive symptoms. Primary obsessive symptoms according to the Y=BOCS checklist were: contamination obsessions (54.7%) and obsessions with need for symmetry and exactness (34.8%). Primary compulsive symptoms were: repeating rituals (46.5 %.) and washing-cleaning compulsions (34.8%).

Patients taking topiramate showed a significant improvement over the 12-week study period (mean Y-BOCS total score at week 12 as compared with baseline: *P*=.000) (Table 2). However, in the placebo group, the Y-BOCS did not improve significantly (*P*=.147). Those receiving topiramate experienced a mean decrease of 32.0% in Y-BOCS score, compared with 2.4% decrease for those receiving placebo. Twelve patients in the topiramate group versus none in the placebo group were rated responder. Comparing to placebo, the topiramate group showed more improvement in all the efficacy measures [efficacy index of CGI (*P*=.000, Z=3.317); Y-BOCS (*P*=.000, Z=3.423); HAM-D (*P*=.000, Z=3.354)].

DISCUSSION

Our study suggests that topiramate may be an effective augmenting agent for the treatment of resistant OCD patients who do not respond to treatment with at least two anti-obsessive medications.

Several lines of evidence from basic neurobiological studies have indicated that glutamatergic abnormalities is associated with OCD symptoms.[5-7] These studies demonstrated pathologically elevated glutamatergic transmission in the cortico-striatal-thalamo-cortical circuit in OCD patients. Following treatment, a decrease in OCD symptom severity was associated with a decrease in caudate glutamatergic concentrations. In this line, topiramate by inhibiting glutamate action via glutamate receptors may exert its anti-OCD action.

Glutamatergic agents successful in treatment of OCD have shown the net effect of reducing glutamate output or signaling. Riluzole and mementine are glutamate antagonists that have been found to be effective in OCD patients.[22-27] Consistent with these studies, our trial showed that topiramat, a glutamate inhibitor, is beneficial for some OCD patients. However, a small trial of lamotigine, a glutamatergic antagonist agent, for OCD refractory patients did not show benefit. Further research using adequate doses of lamotrigine could be of interest in investigation of glutamatergic agents in OCD.[38]

Alternatively, D-cycloserin and glycin act as enhancer of glutamatergic signaling through NMDA receptors, and may exert their anti-OCD effects through actions on the fear extinction circuit of the amygdala that controls anxiety.[29,39,40]

TABLE 1.
Baseline Demographic and Clinical Characteristics of the Patients

	Topiramate Group	*All Placebo*	*Group*
No. of patients	25	49	24
Age (years)	35.4	34.9	33.2
Education (years)	13.0	12.6	12.2
Sex (female)	58.3%	57.1%	55.5%
Duration of illnesses (years)	7.5	8.1	8.7
Y-BOCS	26.5 (3.9)	27.4 (4.1)	28.3 (4.2)
HAM-D	15.9 (4.0)	15.7 (3.9)	15.6 (3.8)

YBOCS=Yale-Brown Obsessive Compulsive Scale; HAM-D=Hamilton Rating Scale for Depression.

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TABLE 2.
YBOCS and HAM-D Scores at Baseline and After 12 Weeks in Topiramate and Placebo Groups

	Topiramate Group		
Placebo Group	**Comparison of**		
The Groups Baseline Mean (SD)	***Baseline 12 Weeks Mean (SD)***	***12 Weeks P value Mean (SD)***	***P value Mean (SD)***
YBOCS	26.5(3.9)	17.9(4.3)	.000
28.3(4.2)	27.6(5.4)	.147	
HAM-D	15.9(4.0)	10.5(2.3)	.000
15.6(3.9)	14.5(2.3)	.181	
CGI		2.1(.47)	.000
3.8(.45)			

YBOC=Yale-Brown Obsessive Compulsive Scale; HAM-D=Hamilton Rating Scle for Depression; CGI=Efficacy Index of Clinical Global.

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In review of literature, two studies investigating the effect of topiramate on OCD symptoms were observed. In a retrospective open study, Van Ameringen and colleagues[41] demonstrated promising therapeutic response to topiramate augmentation strategy. They suggest further investigation using controlled paradigms to better understand the role of topiramate in OCD. The second study was a case report that revealed positive effect of topiramate in a patient with treatment resistant OCD.[42] Our findings are consistent with these pervious reports.

There are some limitations with our study. First, our research is preliminary and larger double blind studies are needed to confirm the results. Second, duration of the trial and dose of the medication used are limited. Longer duration and higher doses of the topiramate may lead to different response rate. For example we stopped at 200 mg/day of topiramate when doses of up to 400 mg/day had been used for psychiatric illnesses before.

CONCLUSION

Our study reveals that topiramate might be beneficial for some patients with treatment resistant OCD. These results add to the literature implicating glutamate in the pathophysiology of OCD and suggest that glutamate-modulating agents may be considered as new pharmacotherapy options. However, the methodological limitations of the study need to be considered. ***CNS***

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