

Original Article

The Comparison of Topiramate and Placebo in the Treatment of Posttraumatic Stress Disorder: A Randomized, Double- Blind Study

Sh. Akuchekian MD*, S.Amanat MD**

ABSTRACT

Background: Posttraumatic stress disorder (PTSD) is a chronic illness and a difficult – to – treat condition. The Hypothesis that exposure to Traumatic events may sensitize or kindle limbic nuclei has led to efforts to treat PTSD with anticonvulsants. Based on the kindling hypothesis of PTSD, this clinical trial was designed to assess the clinical response to topiramate (a new anticonvulsant) as a potential Treatment for PTSD.

Methods: Sixty seven combat veterans with PTSD (range 30-50 years old; SD: 39.5 ± 4.19) randomly assigned in a double – blind design. They were Treated for 12 weeks with topiramate (N=34, 50-500 mg/day) as add – on therapy or placebo (N=33). Patients were monthly assessed for three consecutive months using Clinician – Administered PTSD Scale (CAPS).

Results: Two patients were withdrawn from the study because of topiramate side effects. In reminders, the mean Score of topiramate group, in the first visit was 50.70 ± 7.7 and the mean score of placebo group was 48.9 ± 9.13 . After finishing the treatment period, the mean score of the topiramate group was 32.75 ± 8.2 and of the placebo group was 46.62 ± 8.8 . The analysis of these scores showed a significant difference between the two groups ($P=0.00$). Frequency and intensity of re-experience criteria (intrusive memory, night mare, and flash back), sleep problem, irritability, anger, frequency of difficulty to recall, and intensity of startle reaction in topiramate group was significantly less than placebo group ($P < 0.05$).

Conclusion: The results of this study suggest that topiramate is a safe, well – tolerated, and significantly effective Treatment for PTSD.

Key word: PTSD, Topiramate, Anticonvulsant.

Posttraumatic stress disorder is a syndrome that develops after a person see or hear of an extreme traumatic stressor, or is involved in that¹. Response to a stressor includes reexperiencing a traumatic event, numbed responsiveness or avoidance, and symptoms of an increased level of arousal. Lifetime prevalence of PTSD is estimated to be about 8% of general population, among high risk groups whose members has experienced traumatic events². PTSD is notable among anxiety disorders for its chronicity^{3, 4}, high degree of co- morbidity and associated disability, impaired quality of life, and health-related problems^{5, 6}. Substantial gaps have remained in our understanding of treatment response in PTSD. Hypotheses on the etiology of PTSD have suggested that after exposure to

traumatic events, limbic nuclei may become kindled or sensitized. Consequently, drugs known to have anti-kindling or anticonvulsant effects have been assessed as treatment for PTSD⁷. For example several studies suggest that carbamazepin, Na- valproate, and lamotrigine may be effective in PTSD^{8, 9, 10}. Topiramate is a novel anticonvulsant derived from the naturally occurring monosaccharide D – Fructose¹¹. Topiramate has multiple mechanisms of neural activity, in addition to carbonic anhydrase inhibition¹². Topiramate induces state – dependent blockade of voltage – gated Na channels¹³, enhances GABAergic activity of GABA receptors¹⁴, and exerts a negative modulatory effect on the kainite /AMPA subtype of glutamate receptors¹⁵, and on some high – volt

*Assistant Professor, Department of Psychiatry, Isfahan University of Medical Sciences, Isfahan, Iran

**Assistant Professor, Department of Psychiatry, Isfahan University of Medical Sciences, Isfahan, Iran

Correspondence to: Dr Shahla Akuchekian, Department of Psychiatry, Isfahan University of Medical Sciences, Isfahan, Iran.

age activated Ca channels¹⁶. Other prescription for this drug are the nonepileptic indications such as, mood disorders (e.g. Bipolar I, Bipolar II; as a monotherapy and adjunct medication), eating disorder, and migraine prophylaxis¹⁷. One open Trial has suggested that topiramate may be effective as add-on or monotherapy in chronic PTSD¹⁸.

It has a rapid onset of action and minimal dose-related side effects without the development of tolerance. Few placebo-controlled trials have been reported and recommended double-blind studies. In the present study we tried to investigate the effect of topiramate on combat veterans with chronic PTSD and evaluate the effect of this treatment in chronic PTSD as an add-on trial.

Materials and Methods

This article reports the results of a 12-week double-blind, randomized, add-on and flexible-dose, placebo-controlled study of the efficacy of treatment with topiramate compared with placebo for treatment of PTSD symptoms (their frequency and intensity). The subjects were male outpatient military and combat veterans of Iran-Iraq war who meeting DSM-IV criteria for chronic PTSD and being seen in the Amir-Al-Momenin veterans Administration Medical Center. Written informed consent was obtained from Patients who were eligible to enter the study. Baseline PTSD symptom were rated by the investigator using Clinician-Administered PTSD Scale (CAPS)¹⁹. CAPS is a standard scale which its reliability analysis for assessment of the frequency and intensity of PTSD symptoms are 76% and 83%, respectively. Total reliability for this instrument is 80%. Placebo was made in Pharmacy faculty with the same shape, color, and size as topiramate tablet in 50 mg form. Patients were randomly assigned to receive topiramate or placebo, using random table²⁰.

Inclusion criteria were: chronic PTSD, being treated with psychotropic drugs for at least 6 months, having no response to other medications, and having no kidney disease or stone. Exclusion criteria were: being highly sensitive to medication, and not tolerating the drug side effects. All subjects were evaluated

and rated monthly during 3 months of double-blind treatment, with CAPS.

Topiramate was added to existing pharmacotherapy (such as: Neuroleptic, TCA, BZ, SSRI, Na-valproate, and Carbamazepine with no significant difference between two groups: $P > 0.05$). In most cases, treatment started with dose of 25 mg/day (12.5 mg/day in a few patients, anticipated likely to be highly sensitive to medication) and the dose was increased whenever possible by 25 to 50 mg/day every 3 to 4 days to 500 mg/day or when clinical response developed. The primary outcome measure for the study consisted of the 11-Item severity score of the CAPS which is an investigator-completed assessment instrument that rates the frequency and intensity of PTSD symptoms. Afterwards, data were collected and analyzed using analytic methods such as paired t-test, t-Student, Friedman, and willcoxon with SPSS-II software. A P-value of < 0.05 was considered as statistically significant value.

Results

67 patients participated in a double-blind study for a period of 12 weeks. The patients were male ($N=67$), 30-50 years old (39.8 ± 4.19). The mean of their illness period was 17.9 ± 2.2 years. The events which had caused PTSD in these patients included: 39 cases of explosion wave (58.2%), 7 cases of chemical weapons exposure (10.4%), 5 cases of captivity and torture (7.5%), 14 cases of injury (20.9%), and 2 cases of witnessing the death of their fellow soldiers (3%). The results indicate broad comparability between two groups with respect to demographic features (age, academic level, marriage status, and type of existing pharmacotherapy). All of 67 patients entering treatment (34 on topiramate, 33 on Placebo), returned at least once after treatment began and thus furnished usable data. Patients accountability at each major time point was as follow: month 1, $n=66$; month 2, $n=62$; month 3, $n=62$. Of the 5 drop-outs, 3 came from the placebo group, whereas 2 came from the topiramate group. Reason for drop-out in the topiramate group included drug side ef-

fects such as sexual dysfunction, light headedness, and dizziness (n =2). Subjects in the placebo group dropped out owing to hospitalization (n=2) and lack of efficacy (n=1). The information earned through each visit (4 visits including: the first visit, one month after the treatment, two months after the treatment and three months later) was analyzed by Friedman test (intra rating). During this test, the improvement, caused by Topiramate or Placebo was analyzed from the beginning until the end of the treatment period. Our findings, comparing the different criteria mentioned in the questionnaire, showed that; Topiramate, compared to Placebo, reduced the frequency of nightmare and avoidance activities, intensity and frequency of avoidance (thought and feeling), and difficulty to recall, significantly.

In the next stage, the results and data of the consecutive visits, for both Topiramate and Placebo groups were compared by Willcoxon test as follows: The results of the first and second visits, the results of the first and third visits, the results of the first and the fourth visits were compared and showed that, frequency of nightmare, flashbacks, distress to cues, avoidance (activities), and startle reaction in the fourth visit in topiramate group was significantly less than Placebo group (intra rating).

The mean score of intensity and frequency of each item, mentioned in the questionnaire, was

analyzed by t-test in both Topiramate and Placebo groups (inter rating). Only the scores of the fourth visit (at the end of treatment period) were used for calculating the mean scores. The results are shown in table 1, (Intensity) and table 2, (Frequency). According to the results, either intensity or Frequency of most of symptoms, especially of B criteria (reexperience symptoms) and D criteria (hyper arousal symptoms) of DSM IV criteria of PTSD, in the patients under the treatment with Topiramate was significantly less than Placebo group.

Based on the specified score for each item, the score of each questionnaire was calculated for both Topiramate and Placebo groups. Then the mean scores of both groups, in the first visit, were compared by T-independent test. The mean score of the Topiramate group, in the first visit was 50.70 ± 7.7 and the mean score of the Placebo group was 48.9 ± 9.13 . The analysis of these two mean scores by t-test didn't show a significant difference ($P=0.387$).

The mean scores of the both groups after finishing the treatment period were as follows: the mean score of the Topiramate group was 32.75 ± 8.2 and of the Placebo group was 46.62 ± 8.8 . The analysis of these scores by t-independent test showed a significant difference between the two groups ($P=0.00$).

Table1. Comparative efficacy of Topiramate and placebo in treatment of PTSD on CAPS Intensity, end point. Data are mean \pm SD.

Criteria (Intensity)	Topiramate (N= 34)	Placebo (N = 33)	P-Value
Intrusive Memories	1.66 \pm 0.76	2.11 \pm 0.61	0.002
Night mare	1.60 \pm 0.77	2.13 \pm 0.62	0.000
Flash back	1.23 \pm 0.74	1.59 \pm 0.82	0.033
Distress to cues	1.96 \pm 0.86	2.06 \pm 0.83	0.583
Avoidance(thought feeling)	1.38 \pm 0.84	1.62 \pm 0.97	0.226
Avoidance (activities)	1.42 \pm 0.88	1.51 \pm 0.93	0.647
Difficulty to recall	1.68 \pm 0.89	1.95 \pm 0.80	0.137
Sleep problem	1.87 \pm 0.697	2.50 \pm 0.79	0.000
Irritability & Anger	2.4 \pm 0.54	3.14 \pm 0.76	0.000
Difficult concentration	2.24 \pm 0.84	2.28 \pm 0.74	0.818
Startle reaction	1.85 \pm 0.57	2.27 \pm 0.81	0.010

PTSD=Post Traumatic Stress Disease, CAPS = Clinician - Administered PTSD Scale.

Table 2. comparative efficacy of Topiramate and placebo in treatment of PTSD on CAPS frequency, end point Data are mean \pm SD.

Criteria (frequency)	Topiramate (N= 34)	Placebo (N = 33)	P-value
Intrusive Memories	1.75 \pm 0.896	2.0985 \pm 0.82	0.055 *
Night mare	1.55 \pm 0.74	2.13 \pm 0.66	0.000 *
Flash back	1.18 \pm 0.69	1.53 \pm 0.77	0.027 *
Distress to cues	1.82 \pm 0.74	1.89 \pm 0.77	0.663
Avoidance (thought feeling)	1.51 \pm 1.014	1.58 \pm 0.92	0.707
Avoidance (activities)	1.50 \pm 0.99	1.49 \pm 0.88	0.969
Difficulty to recall	1.65 \pm 0.91	2.09 \pm 0.87	0.022*
Sleep problem	2.10 \pm 0.83	2.99 \pm 0.95	0.000 *
Irritability & Anger	2.397 \pm 0.68	2.98 \pm 0.92	0.002 *
Difficult concentration	2.42 \pm 0.92	2.43 \pm 0.89	0.947
Startle reaction	1.93 \pm 0.65	1.977 \pm 0.78	0.781

Discussion

In this study, Topiramate appears to be markedly effective and well tolerated as add-on in patients meeting DSM-IV criteria for PTSD. Topiramate has clinically and statistically significant effects on most measures of criteria of CAPS-Scale, especially on frequency and intensity of B criteria (re-experience symptoms) including, intrusive memory, night mare, flash back, and some of the D criteria (hyper arousal symptoms) including sleep problem, irritability, and anger.

The mean age of the participants in this study was 39.8 \pm 4.19 years. In a similar study on 35 patients, the mean age of patients was 41.1 \pm 9.5. The mean of the time passed from the event in the present study was 17.9 \pm 2.2 years and in another similar study was 18.1 \pm 15.3 year¹⁸.

Due to the fact that all the patients in this study were the wounded and crippled of the war, the stressors causing PTSD in these patients were related to the war, whereas in an open label study, different factors such as physical and sexual trauma, the death of close relatives, accidents, and so on were considered as the reasons for PTSD¹⁸.

In the present study tri-cyclic anti-depressants, benzodiazepines, and anti-psychotic drugs were the most used medications while in a study performed in the United States, SSRI, trazodone, and tri-cyclic anti-depressants had the most use among patients¹⁸.

The results of this study, matches with the results of another study in which 86% of patients

had less night mare after the treatment¹⁸. That open label study shows that Topiramate has a significant effect on the criteria of group B (re-experience symptoms) in PTSD patients.

Since the B criteria (reexperience symptoms) are the central core of PTSD symptoms²¹, the effect of Topiramate on these symptoms is an important progress in the treatment of PTSD.

Considering the fact that, only 2 patients discontinued taking Topiramate because of its side effects, it seems that this medication is well tolerated by patients. In this Add-on study, side effects such as dizziness and light headedness and sexual dysfunction may have been due to the other medications. Aside from this instance, when side effects occurred they were easily managed by dosage reduction or brief hiatus in administration. Other study has shown that Topiramate is well tolerated by patients, especially in the absence of other psychiatric medications¹⁸. Topiramate demonstrated a rapid onset of action at doses considerably lower than those typically used medications for antiepileptic therapy²². Although sodium valporate is able to control many symptoms of group B (reexperiencing symptoms), Topiramate, compared to sodium valporate doesn't have side effects such as weight gain and increasing the risk of diabetes²³.

In treatment of epilepsy, it has shown that this drug is not associated with the hepatic, cardiac, pancreatic, and hematologic toxicity that is observed with Valproate or Carbamazepin.

More studies are required to determine the therapeutic effects of Topiramate as a monotherapy for PTSD and compare it with other recommended medications and long term therapy. In total, from both clinical and economical points of view and considering the present treatment

methods, finding the best treatment method for PTSD is of special importance.

One limitation of this study is that: the patients suffered from highly chronic PTSD (mean duration=17 years), therefore, it is unclear to extent the results of this study generally for treating patients with less chronic or less severe PTSD.

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