Efficacy and Safety of Topiramate Monotherapy in Civilian Posttraumatic Stress Disorder: A Randomized, Double-Blind, Placebo-Controlled Study

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Objective: This double-blind, placebo-controlled trial assessed efficacy and safety of topiramate monotherapy in civilian posttraumatic stress disorder (PTSD).

Method: Outpatients (18–64 years) with DSM-IV non–combat-related PTSD and Clinician-Administered PTSD Scale (CAPS) scores ≥ 50 were eligible. Topiramate was started at 25 mg/day and titrated by 25–50 mg/week to 400 mg/day or maximum tolerated dose. Data were collected between April 26, 2002, and February 4, 2004. Primary efficacy, change in total CAPS score, and secondary efficacy measures were assessed by analysis of covariance in the intent-to-treat (ITT) population with last observation carried forward.

Results: The ITT population comprised 38 patients with mean ± SD baseline total CAPS scores of 88.3 ± 13.8 (topiramate, N = 19) and 91.1 ± 13.7 (placebo, N = 19). Although a decrease in total CAPS score was noted (topiramate, –52.7; placebo, –42.0), this difference was not statistically significant (p = .232). Topiramate-treated patients exhibited significant reductions in reexperiencing symptoms (CAPS cluster B: topiramate, 74.9%; placebo, 50.2%; p = .038) and Treatment Outcome PTSD scale (topiramate, 68.0%; placebo, 41.6%; p = .025). Reductions approaching statistical significance, based on a nominal p value, were noted in mean total Clinical Global Impressions-Improvement Scale scores (topiramate, 1.9 ± 1.2; placebo, 2.6 ± 1.1; p = .055).

Conclusion: These preliminary results suggest that further, adequately powered studies of topiramate for the treatment of civilian PTSD are warranted.

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Posttraumatic stress disorder (PTSD) is an anxiety disorder that causes individuals significant levels of distress and functional impairment. Diagnostic criteria for PTSD include a history of exposure to a traumatic event leading to intense fear and symptoms from each of 3 symptom clusters: intrusive recollections (cluster B), avoidance/numbing (cluster C), and hyperarousal (cluster D).[1] Recent data estimate lifetime PTSD prevalence to be 10.9%,[2] with up to 40% having a chronic form that is prolonged, may be unremitting, and is subject to reactivation upon exposure to stressors.[3] Treatment of PTSD is often complicated by the presence of comorbid anxiety, mood, and substance use disorders as well as somatic diseases.[4,5]

Recent scientific advances have elucidated the neurobiology of PTSD, which includes a complex, multifaceted interplay of changes or differences in neuroendocrine systems, brain structure and function, and physiologic reactivity.[5] Pharmacotherapeutic treatment of PTSD has been substantiated by few placebo-controlled trials, with open

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trials and case study examples predominating in the literature.[5,6] Although serotonin reuptake inhibitors are most widely studied for the treatment of PTSD, only sertraline[7] and paroxetine[8] are approved by the U.S. Food and Drug Administration for this condition.[5,6] More recently, anticonvulsant agents (e.g., carbamazepine, lamotrigine, divalproex, tiagabine, and topiramate) have increasingly been evaluated for their potential therapeutic role.[5,6]

One theory behind the possible mechanism of action of anticonvulsants in treating PTSD could be related to their antikindling effects.[9] Limbic nuclei may become abnormally sensitized after traumatic events, resulting in increased susceptibility to physiologic arousal and psychiatric disturbance. Because some anticonvulsant agents, including topiramate, may have antikindling effects, potential applications of these agents for PTSD symptoms have been suggested.[9–11] Topiramate's broad-spectrum effects on both inhibitory and excitatory neurotransmitter functions and its antikindling effects may promote symptom reduction in PTSD. Topiramate stabilizes and reduces neuronal hyperexcitability through multiple proposed mechanisms of action, which include enhancement of inhibitory effects of γ-aminobutyric acid,[12,13] blockade of excitatory effect of glutamate through actions at non–*N*-methyl-D-aspartate receptors,[12,14] limitation of repetitive firing of neurons by a state-dependent sodium channel blockade mechanism,[12,15] reduction in calcium channel activity,[16] and inhibition of carbonic anhydrase.[12,13]

Currently, the literature is limited with regard to examining the role of topiramate in civilian, non–combat-related PTSD.[17,18] The objective of this study was to investigate the efficacy and safety of topiramate in this patient population. This trial represents the first published double-blind, placebo-controlled study evaluating topiramate in civilian, non–combat-related PTSD.

METHOD

Patients participated in this study between April 26, 2002, and February 4, 2004, conducted at our outpatient mental health setting associated with the University of Oklahoma Health Sciences Center, Oklahoma City. Selection criteria included men and nonpregnant women 18 to 64 years of age with a diagnosis of civilian, non–combat-related Axis I PTSD for greater than 6 months according to *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) criteria[1] as measured by Structured Clinical Interview for DSM-IV (SCID-IV)[19] and with a Clinician-Administered PTSD Scale[20] (CAPS) score ≥ 50. Women had to be postmenopausal or practicing reliable contraception. Patients with major organic psychiatric disease, current substance dependence or abuse (excluding nicotine or caffeine), serious or unstable concurrent illness, medical conditions potentially affecting drug absorption, history of nephrolithiasis or seizures, reduced renal clearance, elevated serum liver enzyme levels, current enrollment in cognitive-behavioral therapy program, a history of primary major depressive disorder or primary major anxiety disorder, or known hypersensitivity to or a prior adverse event with topiramate were excluded from the study. Pregnant or lactating women were also excluded.

This was a single-center, outpatient, randomized, double-blind, placebo-controlled, parallel-group study that consisted of 3 phases: washout/screening (up to 30 days before randomization), double-blind (titration ≤ 8 weeks and maintenance ≥ 4 weeks, totaling 12 weeks), and taper (~1 week). Study medication was started at 25 mg/day and was titrated by 25–50 mg/week during an 8-week period following a designated washout period for protocol-prohibited medications, which included all psychotropic medications. Patients were randomly assigned to receive either placebo (N = 20) or topiramate (N = 20) in a 1:1 ratio using computer-generated codes; randomization was balanced using permuted blocks.

Patients were titrated to their maximum tolerated dose until complete or nearly complete efficacy was achieved or until the maximum dose allowed (400 mg/day) was reached. Topiramate was given twice daily. All patients provided written informed consent, and approval was received for this study by the Biomedical Research Institute of America and an Institutional Review Board of the University of Oklahoma Health Sciences Center. The study was conducted in compliance with the Declaration of Helsinki.

The primary efficacy variable was the change in the total score of the 17-item CAPS from baseline to the last visit of the double-blind phase, reflecting severity of PTSD. Proposed severity ranges for the total CAPS scores are as follows: 0–19 = asymptomatic or few PTSD symptoms, 20–39 = subthreshold to mild, 40–59 = threshold to moderate, 60–79 = severe, > 80 = extreme PTSD symptoms. In this study, remission was defined as CAPS total score < 20.[31] Secondary efficacy variables consisted of changes from baseline to last visit of the double-blind phase in Hamilton Rating Scale for Anxiety,[21] Hamilton Rating Scale for Depression,[22] Treatment Outcome PTSD scale (TOP-8),[23] Clinical Global Impressions scale (CGI),[24] Davidson Trauma Scale,[25] Barratt Impulsiveness Scale,[26] Sheehan Disability Scale,[27] Connor-Davidson Resilience Scale,[28] and Changes in Sexual Functioning Questionnaire.[29] Safety assessments included monitoring vital signs, clinical laboratory parameters, and adverse events. Adverse events were coded according to the World Health Organization Adverse Reaction Terms.[30]

Efficacy was analyzed in the intent-to-treat population that included all randomized patients who had taken ≥ 1 dose of study medication and had ≥ 1 postbaseline efficacy evaluation. The primary efficacy analysis for the

Table 1. Disposition of Patients With Civilian Posttraumatic Stress Disorder

Group	Topiramate	Placebo
Randomized, N	20	20
Safety, N (%)[a]	19 (100)	19 (100)
Intent-to-treat, N (%)[a]	19 (100)	19 (100)
Completed, N (%)	14 (74)	16 (84)
Withdrawn, N (%)	5 (26)	3 (16)
Adverse event	4 (21)	3 (16)
Patient choice	1 (5)	0 (0)

[a]One patient in each group did not have ≥ 1 post-randomization safety or efficacy measure.

Table 2. Demographics and Baseline Characteristics of Patients With Civilian Posttraumatic Stress Disorder

Variable	Topiramate, N = 19	Placebo, N = 19
Age, mean ± SD, y	42 ± 12	41 ± 9
Sex, N (%)		
Men	4 (21)	4 (21)
Women	15 (79)	15 (79)
Race, N (%)		
White	18 (95)	16 (84)
Black	0 (0)	2 (11)
Other	1 (5)	1 (5)
Comorbid Axis I diagnosis, N (%)		
Major depression	12 (63)	11 (58)
Major depression + panic	5 (26)	6 (32)
Major depression + dysthymia	0 (0)	1 (5)
Trauma type, N (%)		
Childhood sexual abuse	4 (21)	5 (26)
Childhood physical abuse	0 (0)	3 (16)
Domestic/other violence	4 (21)	3 (16)
Rape	2 (11)	2 (11)
Motor vehicle accident	3 (16)	1 (5)
Death/injury of loved one	4 (21)	2 (11)
Witness death	0 (0)	2 (11)
Tornado	3 (16)	0 (0)
Other	1 (5)	5 (26)

change in CAPS score (comparison between treatment groups) was based on an analysis of covariance (ANCOVA) model using treatment as qualitative factor and baseline CAPS score as covariate. For the secondary efficacy variables, ANCOVA analysis was performed using treatment as qualitative factor and baseline score as covariate. ANCOVA was also performed for CGI using treatment as qualitative factor and its baseline score as covariate. All statistical tests were 2-sided, and treatment group comparisons were performed at a significance level of .05. Sample size was not based on statistical considerations. A retrospective power analysis computed the probability of achieving significance with this sample size assuming the population differences in means and standard deviations were the same as the observed values in the study. Based on the ANCOVA for the primary efficacy parameter CAPS total score change from baseline, the retrospective power of the study is about 20%. The analyses on secondary efficacy parameters are all exploratory in nature, and there were no adjustments made for multiplicity.

Table 3. Mean ± SD Percentage Change of Efficacy Measure Scores at Final Visit

Measure	Topiramate,[a] N = 19	Placebo, N = 19	p Value[a]
Primary efficacy measure			
Clinician-Administered PTSD Scale	–59.5 ± 35.9	–45.5 ± 34.3	.227
Secondary efficacy measures			
Hamilton Rating Scale for Anxiety	–53.9 ± 42.8	–40.0 ± 44.2	.331
Hamilton Rating Scale for Depression	–50.7 ± 45.6	–33.3 ± 46.8	.253
Treatment Outcome PTSD Scale	–67.9 ± 30.0	–41.6 ± 37.8	.023
CGI-Severity of Illness Scale	–43.3 ± 27.4	–30.3 ± 28.9	.163
CGI-Improvement Scale	1.9 ± 1.2	2.6 ± 1.1	.069
Davidson Trauma Scale	–54.1 ± 35.8	–32.3 ± 34.8	.065
Barratt Impulsiveness Scale	–3.6 ± 12.5	–4.2 ± 9.4	.868
Sheehan Disability Scale	–30.6 ± 56.4	–35.4 ± 61.9	.804
Connor-Davidson Resilience Scale	11.75 ± 14.0	11.12 ± 17.8	.904
Changes in Sexual Functioning Questionnaire	2.58 ± 31.2	16.2 ± 20.4	.120

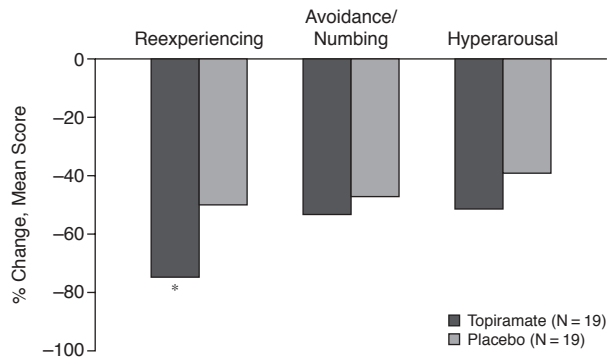
[a]Based on independent t test.
Abbreviations: CGI = Clinical Global Impressions, PTSD = posttraumatic stress disorder.

RESULTS

The efficacy and safety population comprised 38 patients (topiramate, N = 19; placebo, N = 19). The disposition of patients and reasons for withdrawal are provided in Table 1. Demographic characteristics, comorbid Axis I conditions secondary to PTSD, and trauma type were similar between treatment groups (Table 2). Mean ± SD baseline total CAPS scores were 88.3 ± 13.8 (topiramate, N = 19) and 91.1 ± 13.7 (placebo, N = 19), rated extreme in symptomatology based on severity score ranges from clinical research over the past decade (CAPS > 80).[31] Median final dose of topiramate was 150 mg/day (range, 25–400 mg/day), and the mean topiramate treatment duration was 76.0 ± 26.3 days.

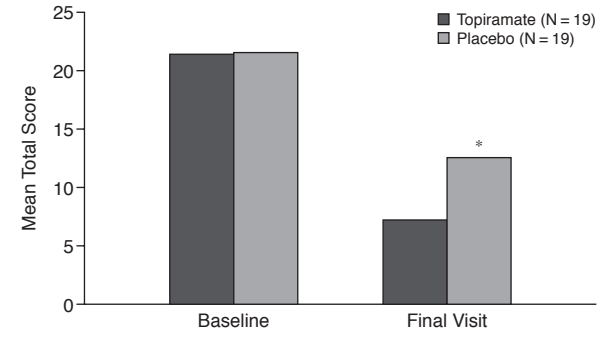
A decrease in total CAPS score from baseline was noted (topiramate, –52.7; placebo, –42.0), but this difference did not reach statistical significance (p = .232). A summary of mean percentage change at final visit of total CAPS overall severity scores and secondary efficacy measures is shown in Table 3. Responder analysis revealed that twice as many patients in the topiramate group (N = 8, 42%) versus the placebo group (N = 4, 21%) achieved remission, as evident by final CAPS scores < 20 (p = .295, effect size = 0.23). Patients in the topiramate group exhibited significantly greater reductions compared with the placebo group in reexperiencing (CAPS cluster B: topiramate, 74.9%; placebo, 50.2%, p = .038; Figure 1) and TOP-8 overall severity (topiramate, 68.0%; placebo, 41.6%; p = .025; Figure 2). Reductions that approached statistical significance, based on a nominal

Figure 1. Percentage Change From Baseline of Mean CAPS Subscale Scores[a] at Final Visit in Patients Receiving Topiramate or Placebo



[a]Cluster B, reexperiencing; Cluster C, avoidance/numbing; Cluster D, hyperarousal.
*p = .038 for topiramate vs. placebo.
Abbreviations: CAPS = Clinician-Administered PTSD Scale, PTSD = posttraumatic stress disorder.

Figure 2. Mean Total Overall Severity Scores of Treatment Outcome PTSD Scale at Baseline and Final Visit in Patients Receiving Topiramate or Placebo



*p = .025 for topiramate vs. placebo.
Abbreviation: PTSD = posttraumatic stress disorder.

p value, were noted in the topiramate group compared with placebo in mean total CGI-Improvement Scale (CGI-I) scores (topiramate, 1.9 ± 1.2; placebo, 2.6 ± 1.1; p = .055), although no improvement in CGI-Severity of Illness (CGI-S) scores was detected.

Discontinuations due to adverse events were as follows: topiramate, N = 4, 21%; placebo, N = 3, 16% (Table 1). Adverse events occurring in ≥ 20% of patients are summarized in Table 4. The most common treatment-emergent adverse events with topiramate, occurring more frequently than with placebo, were headache (N = 7, 37%), sinusitis (N = 5, 26%), and taste perversion (N = 5, 26%). Treatment-limiting adverse events in the topiramate group were emotional lability (N = 1, 5%), nervousness (N = 4, 21%), rectal bleeding (N = 1, 5%), and aggravated depression (N = 2, 11%). There were no meaningful differences

Table 4. Adverse Events Occurring in ≥ 20% of Patients

Adverse Event	Topiramate, N (%)	Placebo, N (%)
Headache	7 (37)	5 (26)
Sinusitis	5 (26)	2 (11)
Taste perversion	5 (26)	0 (0)
Language problems	4 (21)	3 (16)
Insomnia	4 (21)	3 (16)
Dyspepsia	4 (21)	2 (11)
Paresthesia	4 (21)	1 (5)
Nervousness	4 (21)	1 (5)
Fatigue	4 (21)	0 (0)
Hypertension	2 (11)	4 (21)
Difficulty with concentration/attention	2 (11)	4 (21)

between treatment groups in any laboratory test or vital sign parameter during the study. Mean baseline weight was high in both groups (topiramate, 84.8 ± 16.7 kg; placebo, 89.8 ± 26.2 kg). The topiramate group experienced a greater mean change in weight than the placebo group (–1.8 ± 3.3 kg vs. –1.1 ± 2.6 kg, respectively), although this difference was not statistically significant (p = .434).

DISCUSSION

This report represents the first double-blind, placebo-controlled study evaluating topiramate monotherapy in civilian, non–combat-related PTSD. Limited experience with other antiepileptic agents suggests efficacy of these agents in the treatment of PTSD; a few case studies and open-label observations with carbamazepine,[32–34] valproic acid,[32,35–37] and gabapentin[38] and one small randomized, double-blind trial with lamotrigine[39] examine this therapeutic application.

Limited data exist investigating the role of topiramate in civilian, non–combat-related PTSD. In a recent 4-week prospective, open-label investigation evaluating topiramate monotherapy or adjunctive therapy in 33 civilians with chronic PTSD,[17] PTSD Checklist-Civilian Version total symptoms declined by 49% at week 4 (paired t test, p < .001), with similar subscale reductions for reexperiencing, avoidance/numbing, and hyperarousal symptoms. The response rate at week 4 was 77%. Another 4-week prospective, open-label investigation evaluating topiramate as monotherapy or adjunctive therapy in 35 civilians with chronic PTSD[18] noted similar results, documenting a decrease in nightmares and flashbacks in 79% and 86% of patients, respectively, with full suppression in 50% and 54% of patients with these symptoms.

Limited data also exist examining the role of topiramate in combat-related PTSD. A recent double-blind, placebo-controlled study of topiramate augmentation therapy in 40 combat veterans with chronic PTSD failed to find significant treatment effects versus placebo, possibly due to characteristics of the specific population investigated or a high discontinuation rate (topiramate,

55%; placebo, 25%) (S. E. Lindley, Ph.D., M.D., written communication, Dec. 21, 2006).

The limitations of this study include low statistical power, which affected analyses of treatment responses. For each result, the corresponding p values are reported as a measure of the probability that the difference could be attributed to chance alone. Although a reduction in CAPS total severity scores was noted in topiramate-treated patients, this difference did not reach statistical significance. Patients in the topiramate group exhibited significant reductions in CAPS Cluster B reexperiencing symptoms and TOP-8 overall severity scores, and reductions approaching statistical significance were noted in mean total CGI-I and Davidson Trauma Scale scores. As the CAPS, TOP-8, and CGI are rated by clinicians and the first 2 specifically assess PTSD severity, it is unclear why the TOP-8 performed better than the CAPS, unless the brevity of the TOP-8 was a factor. The Davidson Trauma Scale, a self-report instrument assessing severity of PTSD symptoms, did not achieve statistical significance. While analysis of CAPS versus other PTSD measures generally reflects a correlation between clinician report and patient self-report data, neither our study nor a recent study of sertraline[7] showed consistent results between clinician and patient ratings. The extent to which degree of symptomatology, comorbidity, and trauma type impact clinical outcomes also warrants further exploration.[8] Comorbid Axis I diagnoses were present in approximately 90% of this population, which is consistent with other reports.[4] In topiramate-treated patients, trauma type most frequently documented included childhood sexual abuse (21%), domestic or other violence (21%), and death or injury of a loved one (21%). In our study, participants taking placebo had a 45.5% reduction of total CAPS score. This relatively high rate of improvement on placebo is in line with other large trials, with placebo response rates of 40% in a paroxetine study[8] (response defined as 1 or 2 on CGI-I[24]) and 62% in a fluoxetine trial[40] (response defined as 1 or 2 on Duke Global Rating for PTSD[40,41]).

The overall discontinuation rates (topiramate, 26%; placebo, 16%) were lower than in multisite studies with paroxetine[8] and sertraline.[7] However, the apparently higher discontinuation rate due to adverse events may have been due in part to limiting discontinuation reports to 2 categories rather than separately listing other reasons that may have been related to drug effects (e.g., lost to follow-up, laboratory abnormality, protocol violation, other).[7,8]

Studies investigating pharmacotherapy for PTSD treatment are clinically relevant given the epidemiologic evidence that many patients do not achieve symptom remission after years of illness.[4] The long-term implications of pharmacologic treatment on PTSD require future study. Whereas complex clinical histories and clinical characteristics are commonly attributed to PTSD populations, it remains uncertain what impact these variables have on treatment outcomes and what needs exist for further individualization of treatment strategies. In addition, evaluation of treatment responses of different types and durations of traumatic experiences may serve to further elucidate the pathophysiology of this complex disorder.

To date, the ability to generalize findings between combat- and non–combat-related PTSD populations has not been established. Preliminary results from this study therefore represent a significant addition to the limited literature examining the role of topiramate in civilian, non–combat-related PTSD and suggest that further, adequately powered studies of topiramate for the treatment of PTSD are warranted. As the current study is 1 of 3 with similar designs that were conducted in different centers with varying patient populations (civilian and combat-related PTSD), investigators are exploring the possibility of pooling results to acquire an analysis that will be adequately powered.

Drug names: carbamazepine (Equetro, Carbatrol, and others), divalproex (Depakote), fluoxetine (Prozac and others), lamotrigine (Lamictal), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft), tiagabine (Gabitril), topiramate (Topamax).

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