Open-Label Topiramate as Primary or Adjunctive Therapy in Chronic Civilian Posttraumatic Stress Disorder: A Preliminary Report

Jeffrey Berlant, M.D., Ph.D., and Daniel P. van Kammen, M.D., Ph.D.

Background: The hypothesis that exposure to traumatic events may sensitize or kindle limbic nuclei has led to efforts to treat posttraumatic stress disorder (PTSD) with anticonvulsants. Based on the kindling hypothesis of PTSD, this open-label study assesses clinical response to topiramate as a potential treatment for DSM-IV PTSD.

Method: A naturalistic data review was conducted of medical records of all adult outpatients (9 men, 26 women symptomatic for a mean ± SD of 18 ± 15 years with DSM-IV chronic civilian PTSD) treated with topiramate, 12.5 to 500 mg/day, as add-on (N = 28) or monotherapy (N = 7). The last 17 patients completed the PTSD Checklist–Civilian Version (PCL-C) before treatment and at week 4. Dosage titration started at 12.5 to 25 mg/day and increased in 25- to 50-mg increments every 3 to 4 days until a therapeutic response was achieved or the drug was no longer tolerated. The mean duration of treatment was 33 weeks (range, 1–119 weeks).

Results: Topiramate decreased nightmares in 79% (19/24) and flashbacks in 86% (30/35) of patients, with full suppression of nightmares in 50% and of intrusions in 54% of patients with these symptoms. Nightmares or intrusions partially improved in a median of 4 days (mean = 11 ± 13 days) and were fully absent in a median of 8 days (mean = 35 ± 49 days). Response was seen in 95% of partial responders at a dosage of 75 mg/day or less, and in 91% of full responders at a dosage of 100 mg/day or less. Mean reductions in PCL-C score from baseline to week 4 were highly significant (baseline score = 60 vs. week 4 score = 39, $p < .001$), with similar reductions in reexperiencing, avoidance, and hyperarousal criteria symptoms. Thirteen patients discontinued for various reasons during the > 2-year study period. Except for a single instance of acute secondary narrow-angle glaucoma, there were no serious side effects.

Conclusion: Topiramate appeared effective as add-on or monotherapy for chronic PTSD. It demonstrated a rapid onset of action and minimally serious, dose-related side effects without the development of tolerance. Double-blind studies are indicated.

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Received August 15, 2000; accepted May 24, 2001. From the Department of Psychiatry, University of Washington, Seattle (Dr. Berlant); and R. W. Johnson Pharmaceutical Research Institute, Raritan, N.J., and the University of Pittsburgh, Pittsburgh, Pa. (Dr. van Kammen).

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Reprint requests to: Jeffrey Berlant, M.D., Ph.D., 4477 Emerald, Suite A-300, Boise, ID 83706 (e-mail: jberlant@pol.net).

Chronic posttraumatic stress disorder (PTSD) is a difficult-to-treat condition. To date, the U.S. Food and Drug Administration (FDA) has approved only 1 medication, sertraline, for the treatment of 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 antikindling or anticonvulsant effects have been assessed as treatments for PTSD.[1–3] For example, several case reports and open trials suggest that carbamazepine and valproate may be effective in PTSD.[4–8] Treatment with carbamazepine may reduce reexperiencing and arousal symptoms, whereas valproate may reduce avoidance/numbing and arousal symptoms but not reexperiencing symptoms.[9] Furthermore, a double-blind, placebo-controlled trial of lamotrigine in 14 patients with PTSD found that lamotrigine was superior to placebo for intrusion and avoidance/numbing symptoms.[10]

Topiramate is a structurally novel anticonvulsant that contains a sulfamate moiety and is derived from the naturally occurring monosaccharide D-fructose.[11] Topiramate has proven efficacy in the treatment of a broad range of seizure types in adults and children.[12–18] The drug has multiple mechanisms of neural activity. In addition to carbonic anhydrase inhibition,[11,19] topiramate induces state-dependent blockade of voltage-gated Na^+ channels,[20–24] enhances GABAergic activity at $GABA_A$ receptors,[25,26] and exerts a negative modulatory effect on the kainate/AMPA subtype of glutamate receptors [27,28] and on some high-voltage–activated Ca^{2+} channels.[29] In some studies, the activity of topiramate was found to be influenced by

Table 1. Concomitant Medications Received at Baseline[a]

Drug Combination[b]	All Patients (N = 35)	Patients With Nonhallucinatory PTSD (N = 28)	Patients With Hallucinatory PTSD (N = 7)
None	7	7	0
SSRI or venlafaxine	7	6	1
SSRI plus trazodone	1	1	0
Non-SSRI antidepressant	3	3	0
1 anticonvulsant	2	2	0
2 anticonvulsants	2	2	0
Lamotrigine plus selegiline	1	1	0
Valproate plus venlafaxine	1	0	1
Atypical neuroleptic plus valproate	3	1	2
Atypical neuroleptic plus valproate plus lithium	1	0	1
Atypical neuroleptic plus non-SSRI antidepressant	2	0	2
Atypical neuroleptic plus lamotrigine	1	1	0

[a]Abbreviations: PTSD = posttraumatic stress disorder, SSRI = selective serotonin reuptake inhibitor. All values shown as Ns.
[b]Additionally, 8 nonhallucinatory patients received benzodiazepines; 7 nonhallucinatory patients received tramadol, donepezil, or stimulants; and 1 hallucinatory patient received methadone.

the phosphorylation state of the receptor-channel complex.[27] This finding provided the basis for a working hypothesis that topiramate interacts with phosphorylation sites on some receptor-channel complexes and thereby modulates the flux of current through the channels.[30] Although topiramate appears to have a unique mechanism of action, it modulates the same receptor-channel systems that other broad-spectrum anticonvulsants act upon, including carbamazepine and valproate.[31] Since topiramate has also been shown to inhibit kindling in animal models,[32,33] its antikindling properties raise the potential for treatment of PTSD.

METHOD

The study included consecutive patients (N = 35) meeting DSM-IV criteria for chronic PTSD. Of these, 28 had nonhallucinatory PTSD and 7, hallucinatory PTSD. The group with hallucinatory PTSD experienced auditory and/or visual hallucinations containing content specifically associated with identified traumatic events. Whether these were PTSD "flashbacks" or psychotic experiences was at times difficult to ascertain due to patients occasionally being uncertain regarding the reality of the hallucinations. For this reason, prior to being screened for PTSD, some patients had received psychiatric diagnoses of psychotic disorders despite meeting full diagnostic criteria for PTSD.

Topiramate was added to existing pharmacotherapy (see Table 1 for concomitant medications at start of trial), in most cases starting at 25 mg/day (12.5 mg/day in a few patients anticipated likely to be highly sensitive to medication effects) and increasing whenever possible by 25 to 50 mg/day every 3 to 4 days to clinical response. Target symptoms were DSM-IV PTSD criterion B symptoms of nightmares (N = 24) and intrusions (intrusive recollections/flashbacks, N = 35) involving reexperiencing of traumas. Definitions of improvement, as assessed from patient self-report, included "partial response" as "definite reduction in intensity and frequency of nightmares or intrusions" and "full response" as "complete cessation of nightmares and intrusions for a sustained period." After 18 patients had entered the study, the next 17 patients who entered the study completed a self-report scale, the PTSD Checklist–Civilian Version (PCL-C),[34] at baseline and at 4 weeks after starting topiramate in order to systematically identify responsive symptoms. The patients were instructed to complete the PCL-C for experiences corresponding to traumas consistent with DSM-IV criterion A for PTSD. Paired t test scores for the PCL-C were calculated with Jandel SigmaStat v. 2.0 (Jandel Corporation, San Rafael, Calif.).

RESULTS

Patient characteristics are summarized in Table 2. The mean ± SD age at onset of PTSD symptoms was considerably earlier in patients with bipolar disorder (19 ± 14 years) and hallucinatory PTSD (11 ± 5 years) than in nonhallucinatory, nonbipolar patients (29 ± 17 years). Correspondingly, the mean duration of PTSD symptoms was markedly greater in patients with bipolar disorder (21 ± 14 years) or with hallucinations (29 ± 6 years) than in nonhallucinatory, nonbipolar patients (14 ± 16 years). There was no association, however, between duration of symptoms and response to topiramate. Substance abuse, whether past or current at the time of initiation of topiramate, was present in 40% of patients (14/35). Comorbid mood disorders occurred in almost all instances, with a bipolar disorder diagnosis in 10 patients, major depression in 20 patients, and dysthymic disorder in 2 patients.

The primary trauma, as reflected in nightmares and intrusions, most commonly included physical assault and unwanted sexual experience (Table 3). There were no apparent differences in types of primary trauma across patient groupings.

Response assessment, summarized in Table 4, used the last-observation-carried-forward (LOCF) method, which includes all patients who entered the trial and their last reported condition while under active treatment. Overall, topiramate suppressed nightmares in 79% of patients (12/24 fully; 7/24 partially) and intrusions in 86% (19/35 fully; 11/35 partially). In terms of suppression of both nightmares and intrusions (N = 35), 19 patients (54%) reported a full response and 11 patients (31%), a partial response. Five patients discontinued without response, 1 at 5 days and the remaining 4 after 4 weeks. The nonhallucinatory subgroup (N = 28) achieved a higher response rate (full:

Table 2. Patient Demographics[a]

Variable	All Patients (N = 35)	Patients With Nonhallucinatory PTSD			Patients With Hallucinatory PTSD (N = 7)
		Total (N = 28)	Without Bipolar Disorder (N = 20)	With Bipolar Disorder (N = 8)	
Age, y, mean ± SD (range)	41.1 ± 9.5 (21–61)	42.1 ± 9.9 (21–61)	43.4 ± 9.9 (21–61)	38.9 ± 9.7 (21–50)	37.0 ± 7.1 (26–45)
Gender, N	26 F/9 M	22 F/6 M	16 F/4 M	6 F/2 M	4 F/3 M
Age at PTSD onset, y, mean ± SD (range)	24.1 ± 16.6 (3–55)	26.5 ± 16.9 (3–55)	29.1 ± 17.4 (3–55)	19.1 ± 13.6 (5–44)	11.0 ± 4.8 (6–16)
Duration of PTSD, y, mean ± SD (range)	18.1 ± 15.3 (0–45)	16.1 ± 15.8 (0–45)	14.3 ± 16.3 (1–45)	21.1 ± 13.9 (2–38)	29.0 ± 5.6 (22–35)
Other diagnoses, N					
Bipolar disorder	10	8	0	8	2
Major depressive disorder	20	15	15	0	5
Substance abuse, N					
Current	2	1	1	0	1
Past	12	8	5	3	4

[a]Abbreviation: PTSD = posttraumatic stress disorder.

Table 3. Primary Trauma Reflected in Nightmares and Intrusions[a]

Trauma	All Patients (N = 35)	Patients With Nonhallucinatory PTSD (N = 28)	Patients With Hallucinatory PTSD (N = 7)
Physical assault	11	7	4
Sexual assault	5	5	0
Unwanted sexual experience	5	3	2
Sudden unexpected death of someone close	3	3	0
Serious injury or death	2	2	0
Transportation accident	2	2	0
Severe human suffering	2	2	0
Weapon assault	1	0	1
Combat (military or civilian exposure in war zone)	1	1	0
Sudden violent death	1	1	0
Other (eg, death threats to patient and family)	2	2	0

[a]Abbreviation: PTSD = posttraumatic stress disorder. All values shown as Ns.

68%; full/partial: 89%). All full responses occurred in the nonhallucinatory subgroup. Benefit usually occurred within 2 to 3 days of reaching an effective dose. A full response to topiramate was reported for 10 patients within 1 week of treatment and for 3 additional patients by the third week of treatment.

Response was also assessed in 17 patients who completed the PCL-C prior to topiramate therapy and at week 4 of treatment. On the PCL-C, a score of 17 indicates no PTSD symptoms while active PTSD is defined as a score of ≥ 50. The mean total PCL-C scores decreased from 60 ± 10 at baseline to 39 ± 11 at week 4 (range, 17–85, $p < .001$, paired t test). At week 4, 82% of PCL-C scores (N = 14) were below the standardized cutoff score of 50 for active PTSD, 59% (N = 10) were below 40, and 18% of scores (N = 3) were below 30. Subscale score reductions were comparable between baseline and week 4 for criterion B (reexperiencing), criterion C (avoidance), and criterion D (hyperarousal) symptoms: 17 to 10, 25 to 16, and 18 to 13, respectively.

The mean and median time to onset of response by patient group are shown in Table 4. For all patients combined, mean time to onset of partial response for either nightmares or intrusions was 11 ± 13 days with a median of 4 days. For nonhallucinatory patients, mean time of onset was 10 ± 13 days with a median of 4 days. For hallucinatory PTSD patients, mean time was 13 ± 16 days with a median of 7 days. Mean time to onset of a full response for both nightmares and intrusions, which was seen only in nonhallucinatory patients, was 35 ± 49 days, with a median of 8 days. The mean duration of treatment was 33 weeks (range, 1–119 weeks).

Evidence of response was seen at relatively low mean doses of topiramate: response was seen in 95% of partial responders (N = 21) at a dosage of 75 mg/day or less. Response was seen in 91% of full responders (N = 21) at a dosage of 100 mg/day or less. The onset dosage for partial response for the entire sample was 42 ± 32 mg/day (median = 25 mg/day). Lowest onset doses for partial response were attained by nonhallucinatory nonbipolar patients (30 ± 11 mg/day, median = 25 mg/day) and highest doses by hallucinatory PTSD patients (70 ± 51 mg/day, median = 75 mg/day) followed by nonhallucinatory bipolar patients (58 ± 14 mg/day, median = 50 mg/day). For both target symptoms combined, the mean dose required for a full response was 79 ± 114 mg/day (median = 50 mg/day), with a markedly lower dose for nonbipolar (48 ± 25 mg/day, median = 50 mg/day) compared with bipolar patients (154 ± 201 mg/day, median = 38 mg/day). Four of 7 bipolar responders displayed a full response only, thereby lowering the median full response value below the partial response value. Mean dosages for full response were 43 mg/day for monotherapy topiramate (range, 25–75 mg/day) and 97 mg/day for adjunctive topiramate (range, 25–500 mg/day). For partial response,

Table 4. Response to Topiramate[a]

Outcome Measure	All Patients (N = 35)	Patients With Nonhallucinatory PTSD			Patients With Hallucinatory PTSD (N = 7)
		Total (N = 28)	Nonbipolar Disorder (N = 20)	Bipolar Disorder (N = 8)	
Suppression of nightmares (N = 24)	79% (19/24)	84% (16/19)	85% (11/13)	83% (5/6)	60% (3/5)
Partial, N	7	4	2	2	3
Full, N	12	12	9	3	0
Suppression of intrusions (N = 35)	86% (30/35)	89% (25/28)	90% (18/20)	88% (7/8)	71% (5/7)
Partial, N	11	6	3	3	5
Full, N	19	19	15	4	0
Suppression of both intrusions and nightmares (N = 35)	86% (30/35)	89% (25/28)	90% (18/20)	88% (7/8)	71% (5/7)
Partial	11	6	3	3	5
Full	19	19	15	4	0
Time to onset of response, d, mean ± SD (median)					
Partial	10.9 ± 13.1 (4.0)	10.3 ± 12.7 (4.0)	8.6 ± 12.4 (3.5)	17.3 ± 13.5 (17.0)	12.6 ± 15.7 (7.0)
Full	35.3 ± 48.6 (8.0)	35.3 ± 48.6 (8.0)	32.1 ± 44.1 (10.0)	43.3 ± 62.5 (6.0)	…
Dosage of topiramate, mg/d, mean ± SD (median)					
Partial	41.7 ± 31.7 (25.0)	32.8 ± 17.0 (25.0)	26.9 ± 11.2 (25.0)	58.3 ± 14.4 (50.0)	70.0 ± 51.2 (75.0)
Full	78.6 ± 113.8 (50.0)	78.6 ± 113.8 (50.0)	48.3 ± 25.4 (50.0)	154.2 ± 200.9 (37.5)	…

[a]Abbreviation: PTSD = posttraumatic stress disorder.

the mean dosages were 31 mg/day (range, 25–50 mg/day) in the monotherapy group and 46 mg/day (range, 13–150 mg/day) in the adjunctive group. Neither difference between treatment groups was statistically significant (Kruskal-Wallis).

Thirteen patients eventually discontinued treatment: 9 due to side effects (urticaria [N = 1], eating cessation [N = 2], acute narrow-angle glaucoma [N = 1], severe headaches [N = 1], overstimulation/panic [N = 2], emergent suicidal ideation [N = 1], and memory concerns [N = 1]) and 4 for other reasons (patient choice [N = 1], lack of relapse upon medication interruption [N = 2], and lack of efficacy [N = 1]). Five of the discontinuers had experienced full symptom remission prior to discontinuation, and 3 additional patients had reported partial response. Discontinuation rates over the entire observation period were 29% (2/7) in the monotherapy group and 39% (11/28) in the adjunctive group (risk ratio = 0.68, p = NS).

DISCUSSION

This article is, to our knowledge, the first report of a possible effect of topiramate in PTSD. Topiramate appears to be markedly and rapidly effective as add-on or monotherapy in patients meeting DSM-IV criteria for PTSD with prominent criterion B symptoms of trauma-related nightmares or intrusive memories/flashbacks. A high response rate occurred: 86% of patients had a partial or full response when both intrusions and nightmares, if present, were considered together. Although no patient with hallucinatory PTSD exhibited a full response, 79% of nonhallucinatory patients had full responses for both intrusions and nightmares. Within the nonhallucinatory group, 50% of bipolar (4/8) and 75% of nonbipolar patients (15/20) exhibited full response rates, suggesting that the treatment effect of topiramate is independent of any effect on bipolar disorder.

Response to topiramate was not influenced by current or past substance abuse. Topiramate demonstrated a rapid onset of action, often within a few days and usually at doses considerably lower than those typically used for antiepileptic therapy. The difference between mean and median times to onset of response is attributable to at least 2 factors: (1) since this was a naturalistic study, dose changes were occasionally delayed nonsystematically for some patients until their next clinical appointment, and (2) a few patients required relatively higher doses to respond and therefore had a longer time to response. This skewing of the mean time to onset of response also underscores our clinical observation that lack of response at low doses does not preclude response at higher doses.

Experience to date suggests that topiramate markedly suppresses criterion B (reexperiencing) symptoms of PTSD and, although less investigated, criterion C (avoidance) and criterion D (hyperarousal) symptoms as well. We focused on criterion B as an indicator of symptoms that are, in our opinion, central to the core concept of PTSD and readily recognizable by patient and clinician alike. DSM-IV PTSD criterion C and criterion D symptoms can overlap or be confused with depression, agoraphobia, and social phobia. Since the scope of this study was to examine the effect of topiramate on selected prominent core symptoms of PTSD, we believe that, on the basis of our preliminary findings, double-blind, placebo-controlled trials are warranted to analyze the effect of topiramate on all symptom clusters of PTSD and on level of functioning.

Although structured clinical interviews were not used, systematic patient self-reports of the 2 target symptoms were obtained, providing information regarding ordinal changes that are similar to the use of the Clinical Global Impressions–Improvement scale. The first phase of the study included patients in whom the seminal observations were made, bringing the possibility of a positive response to topiramate to our attention. The second phase included systematic use of the PCL-C, a self-report instrument developed and validated by the National Center for PTSD.[34] Using both clinical impression and a self-report scale, there was consistent evidence of a potentially important clinical effect for topiramate.

The reported therapeutic effects of topiramate in PTSD emerged serendipitously during the course of clinical practice. Therefore, in addition to the obvious methodological drawbacks of all open studies, this investigation has limitations in terms of the lack of structured clinical interviews and the use of standardized clinical rating scales in only a portion of the sample. Despite the small sample size, heterogeneity of comorbid psychiatric diagnoses, and presence of concomitant medication in 28 of the 35 patients reviewed, the magnitude and stability of the reported response argue for further study. Controlled clinical trials to investigate the effects of topiramate are warranted, particularly in PTSD populations with less comorbidity, and with expanded attention to other PTSD symptoms, such as difficulty with concentration, which respond poorly to current drug therapies.

In general, topiramate appeared well tolerated in the study population and perhaps even better tolerated in the absence of other medications—an issue to be refined in future studies. Discontinuation due to medication-associated side effects, such as nausea and memory concerns, may have been due to the presence of other medications, to medication interactions, or to individual variation in time needed to accommodate to initial side effects. Subsequent to discontinuation of topiramate, the patient who experienced urticaria continued to complain of unrelated episodes of urticaria. Typical side effects such as dizziness, nausea, or paresthesias were usually transient and, with the exception of nausea and 1 instance of late-onset headache, did not result in discontinuation. The most notable discontinuation involved a single instance of acute narrow-angle glaucoma resulting in emergency ocular surgery and preservation of vision. Although not known at that time to be an associated adverse effect, an ocular syndrome of acute myopia and secondary angle closure glaucoma has since been reported in 23 cases, including the case mentioned here, in the course of postmarketing experience with topiramate including more than 825,000 patients as of August 17, 2001. This ocular syndrome in other cases has remitted when topiramate was discontinued (Joseph Hulihan, M.D., Ortho-McNeil Pharmaceutical, Inc., Professional Letter [on file], September 2001). Aside from this instance, when side effects occurred, they were easily managed by dosage reduction or a brief hiatus in administration.

This report adds to the growing literature on the utility of anticonvulsants for PTSD.[4–10] The preliminary open-label experience with topiramate, based on patient statements and self-rating reports, suggests that there may be a very rapid rate of response to topiramate, with limited risk of harm, and no evidence of tolerance developing over time. Experience with topiramate in the treatment of epilepsy has shown that this drug is not associated with the hepatic, cardiac, pancreatic, and hematologic toxicity that is observed with valproate or carbamazepine. The FDA-approved packaging insert for topiramate does not require or recommend laboratory testing during drug treatment. In addition, topiramate is not associated with weight gain, a complication of valproate use that can increase the risk of diabetes mellitus.[35] Controlled studies will be necessary to ascertain how topiramate compares to other agents in terms of effectiveness. Future research needs to test response differences for all symptoms of PTSD compared with placebo, rates of response compared with other anticonvulsants as well as with antidepressants, comparative side effect profile, and comparative maintenance rates for responders in long-term therapy.

Drug names: carbamazepine (Tegretol and others), donepezil (Aricept), lamotrigine (Lamictal), selegiline (Eldepryl), sertraline (Zoloft), topiramate (Topamax), tramadol (Ultram), venlafaxine (Effexor).

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