

Topiramate in Posttraumatic Stress Disorder: Preliminary Clinical Observations

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© Posttraumatic stress disorder (PTSD) is a serious and debilitating mental condition that affects a significant proportion of the general population at some time in their lives. To date, however, the U.S. Food and Drug Administration has approved only 1 pharmacologic treatment for this indication. Additional effective therapies are urgently required to control the destructive symptoms experienced by individuals with PTSD. This article reviews the effects of the novel antiepileptic drug topiramate on 3 patients meeting DSM-IV criteria for chronic PTSD. In these previously treatment-refractory patients, topiramate had a marked effect: reducing and even eliminating trauma-related intrusive memories and nightmares and normalizing depressed mood. Adverse events were effectively controlled with careful drug titration and discontinuation of concomitant therapies. These findings, together with observations in more than 30 additional patients (reported elsewhere), suggest that further study of topiramate as a treatment for PTSD is warranted. (*J Clin Psychiatry* 2001;62[suppl 17]:60-63)

Posttraumatic stress disorder (PTSD) is a serious, debilitating mental illness. It imposes a tremendous burden on society, not only in relation to its chronic course and frequent comorbidity but also in health care resources and associated costs. Since the recognition of PTSD as a formal disorder in 1980,¹ there has been growing awareness of this medical condition, which affects not only war veterans and disaster victims but also a significant proportion of the general population (as many as 1 in 12 adults)^{2,3} at some time in their lives (see epidemiology review by Breslau⁴ elsewhere in this supplement).

There is an urgent need for effective pharmacologic treatments that can control and reverse the destructive pathophysiologic processes underlying PTSD. To date, only 1 agent (the selective serotonin reuptake inhibitor [SSRI] antidepressant sertraline) has been approved by the U.S. Food and Drug Administration for this indication.

Previously, it has been suggested that drugs known to have antikindling or anticonvulsant effects may be effective in PTSD.⁵⁻⁸ Indeed, some evidence suggests that carbamazepine can reduce reexperiencing and arousal symp-

toms, whereas valproate has shown some efficacy against avoidance/numbing and arousal symptoms of PTSD.⁹

The mechanisms underlying the therapeutic effects of carbamazepine and valproate (i.e., Na⁺ channel blockade and enhanced γ -aminobutyric acid [GABA] neuroinhibition) are also exhibited by the novel antiepileptic drug topiramate. Topiramate has proven efficacy as either add-on or monotherapy in the treatment of a wide range of seizure types in adults and children.¹⁰⁻¹⁶ The drug has an unusually broad spectrum of pharmacologic properties. In addition to Na⁺ channel blockade¹⁷⁻²¹ and enhanced GABA neuroinhibition at GABA_A receptors,^{22,23} topiramate is believed to exert its therapeutic effects via glutamate inhibition at kainate/AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors,^{24,25} inhibition of some high-voltage-activated Ca²⁺ channels,²⁶ and promotion of protein phosphorylation of neuronal conductance channels.²⁴ These properties, together with demonstrated inhibitory activity in animal kindling models,^{27,28} suggest that topiramate may have therapeutic potential in the treatment of psychiatric disorders such as bipolar disorder²⁹ and PTSD.

To date, I have treated 35 adult outpatients meeting DSM-IV criteria for chronic PTSD with topiramate. Findings in this patient sample are reported elsewhere (manuscript submitted). In this article, I review in detail the medical histories of 3 patients from this sample and their respective responses to topiramate therapy.

CASE HISTORIES

Case 1

Ms. A, a 45-year-old woman, presented with occasional "posttraumatic dreams" related to the death of her child

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15 years previously in addition to irritability, depressed mood, impulsivity, and marijuana abuse. Fluoxetine, which had provided some relief for 5 years, had stopped helping. She had been unable to give up cannabis use for 15 years, finding that it helped suppress her nightmares. Preceding the loss of her child, Ms. A had grown up in a household where she remembered feeling terrified and hiding when her parents argued and threatened to kill each other. At the age of 12 years, she was molested by her aunt's husband. When she sought her aunt's intervention, Ms. A was not believed. At 13 years, her father died, leaving her to the care of a "hateful mother," who abandoned her and her sister to live on the street and later with relatives. As she grew older, she found that sex, alcohol, and marijuana provided her with some happiness.

At 29 years, Ms. A became pregnant, only to lose the child to neonatal herpes at the age of 1 week. She described in vivid detail the experience of watching the baby's skin erupt with lesions and then watching as the baby went into cardiac arrest while being attended in an emergency room. She refused to be ushered from the resuscitation room, thereby subjecting herself to viewing the doctors' interventions, which included the futile insertion of a "7-inch needle into the baby's heart." Thereafter, she found herself besieged by nightmares of the death and by intrusive memories of the nightmares. She used alcohol and marijuana to suppress these symptoms for 15 years, but finally decided that she wanted to stop using addictive drugs and come to terms with her problems.

Within 10 days of stopping drugs and alcohol, and despite the introduction of sertraline (50 mg/day), nightmares reemerged every few days, accompanied by near-daily intrusive reexperiencing of the nightmares. Especially troubling were the dreams of seeing her baby's corpse rotting in the ground and calling for her. Accompanying these symptoms were severe startle responses, social avoidance, and very low social functioning.

In view of the severity of her emergent PTSD symptoms, topiramate, 25 mg/day, was added after 2 weeks of treatment. Within 3 days, Ms. A noted that she still had nightmares but that the emotional intensity had lessened. The dreams had become difficult to remember and were no longer "grossly bloody" or filled with references to the decay of her child's body. She felt her emotional reactions to her nightmares were "remarkably low." There were no further daytime intrusive memories or flashbacks of the nightmares. The startling had not occurred. The next night, however, she called to report awakening with an image of her father covered with herpetic lesions. The topiramate dosage was increased to 50 mg/day. The dosage was subsequently reduced to 37.5 mg/day because of feelings of decreased mental clarity and difficulty articulating speech. No further intrusive memories or nightmares and no further adverse effects were experienced with topiramate.

One month later, the dosage of topiramate was decreased to 12.5 mg b.i.d. to determine whether the full dosage was necessary. That night, Ms. A awoke with very severe nightmares of a doctor in an emergency room preparing a needle to inject her baby, a ward clerk yelling at her to provide information about her insurance, and images of herself standing while dripping blood after giving birth. The 37.5-mg/day dosage of topiramate was therefore reinstated. Subsequently, there has been no reappearance of any nightmares or intrusive memories.

Case 2

Ms. B, a 33-year-old woman, was originally seen in consultation for depression during treatment in a substance abuse program. She was found to have major depression, recurrent dysthymia, attention-deficit/hyperactivity disorder, and PTSD. She also experienced bursts of intense persecutory ideation directed toward male drug abusers who she claimed were stalking her. These became so intense that she developed homicidal intent toward one man (independently known to be, in reality, a dangerous cocaine abuser) and purchased a gun to keep on her person at home to use on this alleged perpetrator if he appeared. As her chemical dependency treatment progressed, the story emerged that "religious group" members had exposed her to many years of parentally approved sexual and physical abuse. She also claimed to have intrusive memories of seeing infant sacrifice. She reported many beatings by her siblings and being forced into incestuous activities by several male family members. She was also troubled by learning that her stepfather had secretly videotaped her young daughter and had sold the tapes on the pornographic market.

Several treatments had previously been prescribed, including trazodone, fluoxetine, bupropion, clomipramine, valproate, desipramine, venlafaxine, mirtazapine, thiothixene, and thioridazine. These had been either ineffective or intolerable because of adverse side effects. Without medication, Ms. B was frequently unable to sleep more than 1 or 2 hours due to terrifying nightmares in which she reexperienced these traumas. She had derived partial benefit from paroxetine to help her sleep, and with the support of the chemical-dependency treatment staff, she was placed on methylphenidate treatment with close monitoring. This treatment also decreased her intense anxiety and reduced her emotional overarousal to tolerable levels. As the years of treatment progressed, the claims of recalled memories of infant sacrifice and cult activities drifted away and were solidly replaced with recollections of extensive incestuous and family-condoned sexual abuse by male and female family friends and acquaintances, as well as extensive family violence.

During one episode of several weeks of sustained flashbacks of childhood abuse and insomnia associated with terrifying nightmares incorporating images of childhood violence, topiramate, 25 mg q.h.s., was added to 40 mg

q.p.m. of paroxetine (paroxetine had been maintained at this dosage for over 7 months). Ms. B reported immediate blockade of nightmares and daytime flashbacks, normalization of depressed mood, and increased duration of sleep. This response persisted for nearly 1 month, after which topiramate was discontinued because of the onset of urticaria. Ms. B's PTSD symptomatology remained in remission for approximately 4 weeks and then flared after discussions with her sister regarding their familial sexual abuse.

Since the trial of topiramate 18 months earlier, there had been few periods without active and distressing episodes of reexperiencing symptoms of PTSD. A brief retreat of topiramate was immediately followed by the reappearance of urticarial lesions, but also cessation of active PTSD symptoms and depressed mood for at least 1 month. A subsequent trial of topiramate sprinkle preparation, 15 mg q.p.m., has fully suppressed PTSD symptoms for over a month without urticaria.

Case 3

Mr. C, a 40-year-old married man, was seen after several years of unsuccessful psychiatric treatment with multiple psychiatrists and psychotherapists. He had previously been given multiple diagnoses, including schizophrenia, schizoaffective disorder, bipolar disorder with psychotic features, polysubstance dependence, and recurrent major depression. He also had disabling chronic pain problems with his lower back and severe recurrent migraine headaches.

From adolescence, he had been a heavy drinker and had experimented with various substances including phenylcyclidine, amphetamines, and cocaine. At the insistence of his family and friends, he had stopped drinking 4 years before our first visit, only to develop severe depressive episodes associated with suicidal behavior including medication overdoses. During this 4-year period of abstinence, he was hospitalized for psychiatric treatment 11 times, principally for suicidality. Treatment attempts with several medications, including carbamazepine, diazepam, doxepin, sertraline, alprazolam, zolpidem, trazodone, imipramine, nortriptyline, valproate, olanzapine, and mirtazapine, helped little, if at all.

Although his depressive symptomatology dominated his clinical presentations, with symptoms of severe depressed mood, tearfulness, hopelessness, fatigue, low motivation, and hypersomnia without day/night reversal, Mr. C also experienced prominent anxiety symptoms. He described frequent nightmares of being chased by wolves, falling, and being subjected to physical assault. There were also daily panic attacks and startling associated with flashbacks of images of his father's angry face and of physical abuse by his father. These reexperiencing symptoms were related to several years of childhood sexual and physical abuse inflicted by his father. He found the memories of physical abuse most troubling. Triggers for memo-

ries of abuse included the smell of manure or silage (reminiscent of the sites where he was abused) and looking in the mirror because his face resembled his father's. At times he acknowledged hearing vague sounds of mumbling in the next room, sometimes taking the form of his name being called in a harsh way reminiscent of his father's tone. These symptoms had been present to varying extents for approximately 35 years.

A diagnosis of PTSD was made, and following an explanation of the innovative nature of the treatment and its potential risks and benefits, topiramate was added to Mr. C's regimen of valproate, mirtazapine, and olanzapine. His wife commented that even with the first 25-mg dose of topiramate she was amazed at how peacefully he was sleeping, to the point where she was afraid he had ceased breathing. After 4 hours, the calming effect seemed to wear off, and he began to talk in his sleep and experience awakening. Despite increasing his dosage to 25 mg t.i.d. and reports of a decrease in both intrusive memories and nightmares, an increase in depression and suicidality relating to family issues resulted in his being hospitalized. His inpatient psychiatrist added bupropion, with subsequent improvement in depressed mood.

In the weeks following discharge, mirtazapine, valproate, olanzapine, and benzodiazepine hypnotics Mr. C had received in the hospital were discontinued. Bupropion was continued, and topiramate was increased over 2 months to a dose of 600 mg/day, with a diurnal dosage bias of 50 mg q.a.m. and the remainder, 550 mg, for sleep. He reported that the small morning dose virtually extinguished any daytime intrusions, and the large bedtime dose allowed him to sleep 9 to 10 hours most nights without awakening. Once or twice a week, he still awoke at 5 or 6 a.m. with nightmares of being dead or being verbally abused by his father. He found this tolerable since he was able to fall back to sleep again, something he had previously been unable to do. Thereafter, he was not depressed, felt energetic and motivated, and was no longer suicidal or hypersomnic. Even when additional stressors were introduced (his wife asked him for a divorce once he had improved enough that she felt it was safe to leave him), no further hospitalizations occurred during the 5 months after the topiramate dosage reached 100 mg/day. At this point, administrative considerations resulted in his transfer to another psychiatrist, who has continued him on topiramate treatment.

SUMMARY

In the individuals discussed in this article, topiramate appeared to be markedly and rapidly effective in reducing the symptoms of PTSD, particularly criterion B, reexperiencing symptoms associated with trauma-related nightmares or intrusive memories/flashbacks. It should be noted that these were previously treatment-refractory

patients who had suffered from symptoms related to PTSD for many years (35 years in 1 case) without respite.

The side effects experienced by these patients (decreased mental clarity, difficulty articulating speech, and urticaria) were in the most part effectively controlled following dosage reduction, careful titration, or discontinuation of adjunctive medication.

Taken together with additional data obtained from a sample of more than 30 patients with DSM-IV chronic civilian PTSD (manuscript submitted), these findings argue for further study of topiramate in controlled clinical trials. In particular, further investigation into the effects of topiramate on additional PTSD symptoms that have to date shown little response to medication, such as difficulty with concentration, is warranted.

Drug names: alprazolam (Xanax and others), bupropion (Wellbutrin), carbamazepine (Tegretol and others), clomipramine (Anafranil and others), desipramine (Norpramin and others), diazepam (Valium and others), doxepin (Sinequan and others), fluoxetine (Prozac), methylphenidate (Ritalin and others), mirtazapine (Remeron), nortriptyline (Pamelor and others), olanzapine (Zyprexa), paroxetine (Paxil), sertraline (Zoloft), thiothixene (Navane), topiramate (Topamax), venlafaxine (Effexor), zolpidem (Ambien).

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