Tiagabine for Posttraumatic Stress Disorder: A Case Series of 7 Women

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Background: Posttraumatic stress disorder (PTSD) is often a chronic disorder, and, though 2 antidepressants are now approved by the U.S. Food and Drug Administration for its treatment, it often remains refractory to pharmacotherapy. The memory of traumatic events, by repeatedly stimulating the hippocampus and amygdala (kindling phenomenon), may alter multiple biological systems, including γ-aminobutyric acid (GABA) pathways, and eventually lead to the disorder. Tiagabine, a selective GABA reuptake inhibitor, was evaluated as a treatment for PTSD.

Method: Patients with DSM-IV PTSD who were stable on current medications and still symptomatic were eligible for inclusion in this open-label case series. Tiagabine was initiated at 2 mg nightly and increased by 2-mg increments every 2 to 3 days until an optimal response was achieved. The Clinical Global Impressions-Improvement scale and PTSD Checklist-Civilian Version (PCL-C) were used to evaluate changes in PTSD symptoms.

Results: Seven consecutive female patients were identified as eligible. Tiagabine markedly improved PTSD symptoms within 2 weeks for 6 of the 7 patients, and 6 patients were rated as "much improved" or "very much improved." The mean PCL-C score was significantly reduced at weeks 2 and 8 ($p < .05$) as were the 3 PCL-C subscales and 1 of 2 items related to sleep disturbance. The mean effective daily dosage was approximately 8 mg (range, 4–12 mg/day). Treatment with tiagabine was generally well tolerated.

Conclusions: These preliminary open-label findings suggest that the selective GABA reuptake inhibitor tiagabine may be a promising therapeutic option in the treatment of PTSD. Further study into the efficacy and safety of tiagabine for the treatment of PTSD is warranted.

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Posttraumatic stress disorder (PTSD) is often a chronic and refractory illness, with a lifetime prevalence of approximately 8% in adults in the United States[1] and a higher prevalence in women.[2] Individuals presenting with this disorder have been exposed to a traumatic event and reexperience the event (in the form of distressing images, nightmares, or flashbacks), persistently avoid stimuli associated with the trauma, and have persistent symptoms of increased arousal (sleep problems, irritability).[1] Although 2 antidepressants have recently been approved by the U.S. Food and Drug Administration for its treatment, PTSD remains a difficult treatment challenge for the clinician. This may be due to the complexity of the disorder and the limitations of current treatments related to efficacy, tolerability, and abuse, creating the need for additional therapeutic options.

The process by which intrusive and distressing recollections of a traumatic event produce alterations in biological systems and lead to the development of PTSD has yet to be fully determined. Models have been proposed in an attempt to describe this process, including an adaptation of a neural network model.[3] Included in this model is the kindling phenomenon, where repeated stimulation of brain regions (e.g., hippocampus and amygdala) by traumatic memories leads to progressively increasing responsivity to stressors and eventually the emergence of a disease state.[3,4] The heightened responsivity to stressors is thought to arise from alterations in multiple biological systems, including γ-aminobutyric acid (GABA), the main inhibitory neurotransmitter of the central nervous system.[5]

Evidence for the involvement of GABA in anxiety originated from the use of benzodiazepines ($GABA_A$ receptor allosteric modulators) as treatment. Recently, neuroimaging studies have found decreases in GABA receptor binding/affinity and levels of GABA in patients with various anxiety disorders. Compared with healthy subjects, single-photon emission computed tomographic (SPECT) imaging revealed that PTSD combat veterans had fewer GABA receptors available to bind to radiolabeled iomazenil, particularly in the prefrontal cortex.[6] In 2 similar studies, decreased GABA receptor binding was found in structures relevant to panic disorder (using positron emission tomographic scan technology)[7] and generalized anxiety disorder (using SPECT technology) patients.[8]

Table 1. Baseline Patient Characteristics of 7 Women Treated With Tiagabine for PTSD

Patient	Age, y	Duration of PTSD, y	Comorbid Diagnosis	Prior Medications	Concomitant Medications (mg/day)
1	52	3	Major depressive disorder	Sertraline, bupropion, venlafaxine, citalopram, paroxetine, gabapentin	Fluoxetine (40)
2	31	13	Major depressive disorder	Sertraline, risperidone, prazosin, citalopram, various anxiolytics	Nefazodone (400), prazosin (4)
3	41	26	Major depressive disorder, ADHD	Paroxetine, prazosin	Fluoxetine (20), dextroamphetamine (30)
4	47	30	Major depressive disorder, OCD	Various antidepressants	Buspirone (15), alprazolam (2), nefazodone (150)
5	35	4	Major depressive disorder, panic disorder	Fluoxetine, gabapentin, propranolol, prazosin	Clonazepam (1), nefazodone (200), buspirone (10), propranolol (40), prazosin (2)
6	38	23	Major depressive disorder, panic disorder	Citalopram, sertraline, nefazodone, prazosin	Paroxetine (20)
7	38	18	Bipolar disorder, ADHD	Various antidepressants, various anxiolytics, prazosin	Valproic acid (2000), bupropion (150), dextroamphetamine (30)

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, OCD = obsessive-compulsive disorder, PTSD = posttraumatic stress disorder.

Tiagabine is a selective GABA reuptake inhibitor. Tiagabine selectively increases synaptic GABA availability by blocking the reuptake of GABA via transporter inhibition.[9] In preclinical studies, tiagabine has demonstrated antikindling and antianxiety properties.[10,11] In preliminary reports, tiagabine has shown potential as monotherapy or augmentation therapy for PTSD,[12,13] panic disorder,[14] treatment-resistant anxiety,[15] and generalized anxiety disorder.[16,17] Additionally, tiagabine has been found to improve subjective and objective sleep quality.[16,18] These findings suggest that tiagabine may be useful in the treatment of PTSD.

METHOD

This was an open-label case series involving 7 patients and was conducted in a private practice outpatient clinic. Patients were interviewed and their records reviewed to establish the diagnosis of PTSD and comorbid disorders. To be eligible, patients had to (1) meet DSM-IV criteria[19] for PTSD within the last 6 months, (2) be stabilized on all existing medications but still symptomatic, (3) be free of substance abuse for at least 1 month prior to tiagabine treatment, (4) have no prior history of schizophrenia, and (5) give informed consent to participate in the case series.

Tiagabine was added to existing medication regimens beginning at a dose of 2 mg nightly or divided between a morning and bedtime dose and increased by 2 mg every 2 to 3 days until an optimal response with good tolerability was achieved. Changes in PTSD symptoms were evaluated using 2 measures. With the Clinical Global Impressions-Improvement scale (CGI-I), positive responders are classified as "much improved" or "very much improved."[20] The PTSD Checklist-Civilian Version (PCL-C) is a brief, self-rated questionnaire consisting of 17 items, which can be grouped into 3 subscales corresponding to the 3 DSM-IV symptom clusters for diagnosing PTSD (intrusive recollections, persistent avoidance of stimuli associated with the trauma, and persistent symptoms of increased arousal).[21] Patients were asked to rate the impact of each symptom from "not bothered at all" (represented by a score of 1) to "extremely bothered" (represented by a score of 5). Scores range from 17 to 85. The PCL-C was administered just prior to initiation of treatment with tiagabine (baseline) and after 2 weeks, 8 weeks, and, in some cases, 12 and 16 weeks of continuous tiagabine treatment. The mean changes from baseline on the PCL-C total, subscale, and item scores were compared by paired t test. Patients were asked at all clinic visits to report any adverse events noted during treatment with tiagabine.

RESULTS

Seven consecutive female patients were positively identified as having PTSD, all of whom had 1 or more of the following comorbidities: attention-deficit/hyperactivity disorder (ADHD), bipolar disorder, major depressive disorder, obsessive-compulsive disorder, and panic disorder (Table 1). The mean (SD) age was 40 (7) years and duration of PTSD was 17 (11) years. All 7 women had histories of several unsatisfactory medication trials. Concomitant medications included anxiolytics, antidepressants, antipsychotics, and anticonvulsants.

Tiagabine markedly improved the symptoms associated with PTSD in 6 of the 7 patients (86%). The mean effective daily dosage was approximately 8 mg (range, 4–12 mg/day). Improvements were reported within 1 to 3 days of initiating treatment with tiagabine; after 2 weeks of treatment, all 6 patients showed marked improvement on the CGI-I. Tiagabine significantly decreased the mean PCL-C score from baseline at weeks 2 and 8 (Table 2). Furthermore, significant reductions from baseline on the 3 symptom cluster subscales (intrusive recollections, avoidance, and arousal) of the PCL-C were observed (Table 2).

Table 2. Mean (SEM) Scores on the PCL-C in 7 Women Treated With Tiagabine for PTSD

Score	Baseline	Week 2	Week 8
Total	68.0 (3.2)	41.6 (5.0)*	44.8 (4.0)*
Subscale			
Intrusive recollections	21.0 (1.4)	13.6 (1.5)*	14.0 (1.3)*
Avoidance	27.3 (1.6)	17.0 (2.6)*	17.7 (2.5)*
Arousal	18.7 (1.6)	12.4 (1.5)*	13.2 (1.6)*
Item			
Distressing dreams	3.9 (1.7)	2.8 (1.1)*	2.3 (1.2)*
Difficulty falling or staying asleep	3.8 (0.48)	2.6 (0.40)	2.5 (0.43)*

*$p < .05$.
Abbreviations: PCL-C = PTSD Checklist-Civilian Version, PTSD = posttraumatic stress disorder, SEM = standard error of the mean.

Of the 17 items of the PCL-C, the nightmare (distressing dreams) item showed the most (mean) improvement at weeks 2 and 8 **(**Table 2**)**. The other item associated with sleep disturbances (difficulty falling or staying asleep) was also significantly improved at 8 weeks **(**Table 2). Of the same 6 patients, 5 were found "much improved" and 1 "very much improved" on the CGI-I by weeks 2 and 8 as compared with baseline.

Three patients (see Table 1: patients 2, 3, and 6) evaluated following 12 and 16 weeks of continuous treatment with tiagabine continued to show improvements in PTSD symptoms from baseline. Mean PCL-C total scores were reduced from baseline by approximately 40% at both time points (N = 2). Mean PCL-C intrusive, avoidance, and arousal subscale scores decreased by 36%, 37%, and 27%, respectively. Improvements in mean score on items related to sleep quality did not reach statistical significance at these later time points.

One patient (see Table 1: patient 4) withdrew from treatment with tiagabine due to intense abdominal cramping and diarrhea shortly after initiation of tiagabine, 2 mg nightly. These adverse events were similar to those experienced during her ongoing cancer chemotherapy. Treatment was discontinued for 4 days and then reinstated at 0.5 mg nightly; however, the cramping and diarrhea resumed. Treatment with tiagabine was permanently discontinued.

Three of the 6 patients who had a favorable response to treatment with tiagabine are described below.

CASE REPORTS

Case 1

This 31-year-old, single, white female child daycare employee (see Table 1: patient 2) was raped at the age of 17 by a perpetrator who was convicted but never sentenced (and subsequently released). She experienced acute PTSD symptoms requiring hospitalization for 2 weeks and did not seek further treatment for her PTSD until 10 years later in 1999. Despite counseling, a hospitalization, and trials of sertraline, 100 mg/day, nefazodone, 400 mg/day, risperidone, 4 mg/day, and various anxiolytics, her PTSD symptoms showed little improvement. Since the rape, she felt like she was being followed; was mistrustful, on edge, jumpy, and distracted; and avoided people to the degree that she rarely went out and kept her living room curtains closed at all times. She experienced flashbacks, dissociative states, depression, and intermittent suicidal ideations.

Upon referral to this clinic, she began treatment with prazosin, 4 mg nightly, which resulted in a reduction in the severity of her nightmares only. Citalopram was gradually added up to 20 mg/day, but she experienced visual disturbances, including afterimages, and discontinued treatment. She was afraid to consent to other antidepressant trials but consented to a trial of tiagabine since it was of a different class of compounds. Treatment with tiagabine was initiated at 2 mg nightly and increased to 4 mg nightly after 3 days. She was considered to be "much improved" on the CGI-I, and her PCL-C score decreased from 82 at baseline to 61 following 2 weeks of treatment with tiagabine. Additionally, she reported feeling better than she had felt in years, sleeping soundly, and no longer experiencing trauma-related nightmares, although having normal dreams. Her flashbacks, intrusive memories, startle responses, dissociative episodes, and avoidance behaviors were also improved. Throughout treatment with tiagabine, she reported no side effects. For the first time in 10 years, she was able to return to her hometown in which the rape occurred.

Two months later, the patient attempted to discontinue tiagabine and her PTSD symptoms returned within a week. She resumed her tiagabine regimen and has continued to do well for greater than 5 months, with a 16-week PCL-C score of 59.

Case 2

This 41-year-old, divorced, white female social worker (see Table 1: patient 3) was diagnosed with ADHD in grade school and major depression in 1990. She had experienced severe physical and psychological abuse from birth to 15 years of age, with the physical abuse resulting in permanent bodily scarring. Growing up, her family had moved every several months to evade child protective service agencies, which were called frequently by concerned teachers; she never attended the same school for longer than 9 months. By 1998 her depression had resolved, and the ADHD symptoms were under control with a daily regimen of paroxetine, 20 mg/day, and dextroamphetamine, 30 mg/day.

In 1999 she was raped and experienced discrimination at the workplace, whereupon severe PTSD symptoms emerged. Her symptoms included intense flashbacks, dissociative states, nightmares, frequent nighttime awakenings, vigilance in work/social settings, irritability, and

avoidance of even mild conflict. The addition of prazosin, 1 mg nightly, obliterated her nightmares and sleep disturbances, but treatment had to be discontinued after an episode of syncope and several episodes of near syncope.

Treatment with tiagabine was initiated at 2 mg nightly and increased to 4 mg nightly after 3 days. She reported benefits within 2 days of beginning tiagabine, was able to sleep through the night for the first time in years, no longer experienced trauma-related nightmares, and awoke feeling rested. Daytime PTSD symptoms were somewhat improved, and daytime dosing was requested. A morning dose of tiagabine, 2 mg, was added and later increased to 4 mg, which effectively managed her daytime PTSD symptoms. After 2 weeks of treatment with tiagabine, she was rated as "much improved" on the CGI-I, and her PCL-C score decreased from 68 at baseline to 37. She felt normal for the first time, no longer feared being out of the house, regained her sense of humor, and continued to experience normal dreaming. She did report sedation upon treatment initiation; however, this side effect resolved within 3 days.

The patient has continued to do well for greater than 4 months with tiagabine, 8 mg/day (4 mg in the morning and 4 mg at night), with a 16-week PCL-C score of 29.

Case 3

This 38-year-old, single, white female executive of a large company (see Table 1: patient 7) first presented with bipolar disorder and ADHD, in addition to PTSD, in 1995. Her PTSD symptoms were attributed to sexual abuse from the ages of 8 to 13 years. The symptoms included intrusive memories of the abuse taking place in her childhood bedroom, flashbacks, nightly insomnia, vivid trauma-related nightmares (2–3 per week), fear of going to bed, and a bedtime routine including checking behind furniture and going to sleep with all the lights on.

The symptoms associated with bipolar disorder quickly responded to bupropion hydrochloride, 150 mg/day, and valproic acid, 2000 mg/day. The symptoms associated with ADHD were successfully controlled with dextroamphetamine, 20 mg/day, which was not associated with a worsening of her PTSD symptoms. Her PTSD symptoms did not improve with counseling, valproic acid, 2000 mg/day, 4 trials with different antidepressants, anxiolytics, and a trial of prazosin for nightmare suppression. She reported guardedness, startle responses, and avoidance of movies with even a mild degree of violence and used work to escape the intrusive memories of her past.

Tiagabine was initiated at 2 mg nightly and, after 3 days, increased to 4 mg nightly. She reported improvement within 3 days after beginning tiagabine, including the return of normal sleep patterns, the complete resolution of trauma-related nightmares, the absence of apprehension about sleep, and the presence of normal dreaming. Other PTSD symptoms showed improvement, including fewer intrusive memories and flashbacks, reduced guardedness, and less frequent checking behind furniture. Following 2 weeks of treatment, she was found to be "much improved" on the CGI-I, and her initial PCL-C score was reduced from 70 to 39. She still avoids certain movies and other reminders of the trauma. Sedation was noted within the first several days of treatment; however, this side effect dissipated within a week.

The patient has remained stable on 4 mg of tiagabine taken nightly for greater than 3 months, with a 12-week PCL-C score of 26.

DISCUSSION

The findings of this open-label case series of 7 women suggest that the selective GABA reuptake inhibitor tiagabine may be an effective therapeutic option for symptoms of PTSD. Tiagabine significantly improved the intrusive recollections, avoidance, and arousal characteristics of PTSD. Most patients reported improvements within 3 days of beginning tiagabine treatment, which were maintained for 8 weeks of treatment. Moreover, tiagabine significantly reduced sleep disturbances (distressing dreams and difficulty falling or staying asleep) associated with PTSD. Tiagabine was effective in reducing trauma-related nightmares and improving sleep quality ("sleeping soundly" and "awoke feeling rested") while preserving normal dreaming.

Treatment with tiagabine was well tolerated, with only 1 patient discontinuing treatment due to diarrhea. Perhaps the threshold for this symptom was lowered by her colorectal cancer and the resection and radiation therapy to the colorectal area. The positive response to tiagabine on the anxiety component of PTSD adds to the growing body of literature supporting the use of tiagabine in the treatment of anxiety disorders.[12–17] The ability of tiagabine to improve core characteristics of PTSD (intrusive recollections, avoidance, arousal) is consistent with its mechanism of action. Tiagabine increases GABA in the synapse,[9] which leads to an increase in GABAergic control of neuronal activity[10] and thus reduces the heightened responsivity to stressors.[11] The rapid onset of action of tiagabine suggests that its efficacy relates to the immediate availability of extra GABA within synapses of PTSD-related structures such as the amygdala and hippocampus. All 7 patients were taking concomitant antidepressants, and 6 of the 7 were taking serotonin reuptake inhibitors. This raises the issue of whether tiagabine is effective alone or whether its efficacy derives from the enhancement of ongoing antidepressants.

The improvement in trauma-related nightmares and sleep quality, in addition to the findings that tiagabine improved subjective and objective sleep quality,[16,18] suggests the utility of tiagabine in the treatment of sleep disturbances.

Drugs that modulate the GABA system have been shown to be effective in the treatment of PTSD.[22–25] The distinct and selective mechanism of action of tiagabine in comparison with the other GABAergic agents may serve as a useful probe in furthering our understanding of PTSD pathophysiology. Tiagabine has a short half-life, and, for epilepsy, its duration of action is between 6 and 12 hours. Some of the patients in this case series experienced a reduction of daytime PTSD symptoms even with once a day (evening) dosing. It is possible that the reduction of nightmares and increase of restorative sleep have the effect of contributing to the reduction of daytime symptoms. The alpha-1 adrenoceptor blocker prazosin has a duration of action of about 6 hours, yet several studies show that nightly dosing reduces daytime PTSD symptoms in civilians[26] and veterans.[27]

The positive effect of the selective GABA reuptake inhibitor tiagabine in patients with PTSD is encouraging; however, one must take into account that these observations come from an open-label case series of only 7 patients. Further study of the selective GABA reuptake inhibitor tiagabine for the treatment of PTSD, with special attention to sleep parameters, is warranted.

Drug names: alprazolam (Xanax and others), bupropion (Wellbutrin and others), buspirone (BuSpar and others), citalopram (Celexa), clonazepam (Klonopin and others), dextroamphetamine (Dexedrine, Dextrostat, and others), fluoxetine (Prozac and others), gabapentin (Neurontin and others), nefazodone (Serzone and others), paroxetine (Paxil and others), prazosin (Minipress and others), propranolol (Inderal and others), risperidone (Risperdal), sertraline (Zoloft), tiagabine (Gabitril), valproic acid (Depakene and others), venlafaxine (Effexor).

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