Levetiracetam for Treatment-Refractory Posttraumatic Stress Disorder

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Objective: To assess the use of levetiracetam, a novel anticonvulsant agent, in the treatment of refractory posttraumatic stress disorder (PTSD).

Method: Retrospective analysis was conducted of 23 patients with DSM-IV diagnosis of PTSD who, after being deemed partial or nonresponders to antidepressant therapy, received levetiracetam in a naturalistic fashion. The primary outcome measure was the PTSD Checklist-Civilian Version (PCL-C). Secondary outcome measures included the Hamilton Rating Scale for Anxiety (HAM-A), the Hamilton Rating Scale for Depression (HAM-D), Clinical Global Impressions-Severity of Illness scale (CGI-S), and Clinical Global Impressions-Improvement scale (CGI-I).

Results: Levetiracetam at a mean ± SD dose of 1967 ± 650 mg/day for 9.7 ± 3.7 weeks was generally well tolerated. Nineteen patients (83%) were taking at least 1 concomitant medication. Patients were severely ill with a mean baseline PCL-C score of 67.2 ± 9.4, CGI-S score of 6.0 ± 0.7, and HAM-A score of 26.8 ± 4.9. Patients improved significantly on all measures ($p < .001$). Thirteen patients (56%) met responder criteria at endpoint (PCL-C mean change = 23.5, CGI-I score ≤ 2), and 6 (26%) met remission criteria (CGI-S score ≤ 2). Adverse events were generally mild, and no patients discontinued levetiracetam because of side effects.

Conclusion: These preliminary data suggest that levetiracetam may be an effective treatment in combination with antidepressant therapy for patients with PTSD who remain symptomatic after initial intervention.

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Traumatic stress represents a significant health problem, with estimates of 5% to 35% annual exposure to a traumatic event and a lifetime exposure of 1 or more traumatic events for more than 50% of the U.S. population.[1] Traumatic experiences such as physical and sexual assault, fires, motor vehicle accidents, and natural disasters have been recognized as events that may contribute to the development of posttraumatic stress disorder (PTSD), and this advent has led to an increased awareness of the prevalence of this disorder. Posttraumatic stress disorder affects a significant portion of society and tends to inflict substantial psychiatric comorbidity due to the chronic and refractory nature of the disorder. As such, PTSD represents a significant burden to society, especially with regard to associated escalated levels of psychosocial disability, somatic complications, and utilization of health care resources.[2]

Posttraumatic stress disorder is characterized by specific symptoms that appear after exposure to psychological trauma, including reexperiencing of the event, avoidance of related stimuli, and persistent symptoms of increased arousal.[3] While the pathophysiology of PTSD is not fully understood, it has been suggested that repeated recollection of memories associated with the trauma modifies the structure of the neural networks involved in the processing of traumatic memories.[4] This idea incorporates the psychobiological model of PTSD that involves sensitization of certain brain regions through repeated stimulation by traumatic memories, in a manner similar to the kindling phenomenon seen in epilepsy.[4–6] Such changes in the biological stress response system could result in the symptoms associated with PTSD.

The identification of effective and definitive pharmacotherapy for PTSD is still in a nascent stage, with relatively few medications currently approved for the treatment of this disorder. In particular, there remains an outstanding need for efficacious pharmacologic agents that do not promote weight gain, sexual dysfunction, or affective numbing. In addition, as patients with PTSD have high rates of comorbidity with substance abuse/dependence, an agent that lacks potential for addiction would be optimal.

Despite the effectiveness of available treatments such as selective serotonin reuptake inhibitors as well as

cognitive-behavioral therapy, many patients remain symptomatic despite initial intervention. There are few systematic data available to guide clinical practice regarding the relative benefits of "next step" or "add-on" strategies to manage chronic and refractory patients.

An increasing body of evidence supports the potential efficacy of anticonvulsants for the treatment of anxiety disorders.[7–9] The implication of stress-activated limbic kindling in the pathophysiology of PTSD and the demonstrated antikindling effects of anticonvulsants in the treatment of epilepsy strongly support the potential benefit of such agents for the treatment of PTSD. Prior studies examining anticonvulsants in the treatment of PTSD have produced promising results. In an open-label case series of 7 patients receiving adjunctive tiagabine, 86% of patients exhibited markedly improved PTSD symptoms.[10] Likewise, in an open-label trial of 35 patients receiving adjunctive topiramate, 86% of patients showed a partial or full response.[11] Of 30 patients treated with adjunctive gabapentin in an open-label study, 77% showed moderate or target symptom improvement.[12] Finally, in a randomized, double-blind study of 15 patients receiving either lamotrigine or placebo, 50% of patients receiving lamotrigine responded compared to only 25% of patients receiving placebo.[13]

Levetiracetam is a novel anticonvulsant agent that reduces neuronal transmission through high-voltage–activated calcium channels and has effects at a unique central nervous system binding site.[14,15] Recent evidence suggests that levetiracetam may also exert its effects by modulating a function of the synaptic vesicle protein SV2A present only under pathophysiologic conditions.[16] In 1999, the U.S. Food and Drug Administration approved levetiracetam for use in the adjunctive treatment of adults with partial-onset seizures.[17] The drug has shown a lack of efficacy in the treatment of standard epilepsy models, but has been effective against kindled seizures in animal models,[18] suggesting that it may also be effective in the treatment of PTSD.

Recent animal data suggest that levetiracetam counteracts benzodiazepine withdrawal–induced anxiety in mice.[19] Its potential antianxiety effects were also assessed in a preclinical study[20] in which 5.4 to 54 mg/kg of levetiracetam was administered intraperitoneally to rats. The results showed significant reductions in anxiety-related behavior. Nonclinical study results also showed a different anxiolytic profile for levetiracetam as compared to classical benzodiazepines, potentially suggesting a lower risk for dependence and abuse.[21]

Levetiracetam has a favorable pharmacokinetic profile, with rapid absorption following oral administration, excellent bioavailability, quick attainment of steady-state concentrations, linear kinetics, and minimal plasma protein binding.[22] In the treatment of epilepsy, it has shown minimal adverse effects and low propensity for drug interactions.[17,18] A recent open-label study by Simon and colleagues[23] examined levetiracetam in the treatment of 20 patients with social anxiety disorder. Treatment with levetiracetam was well tolerated, and patients showed a clinically significant improvement in anxiety-related symptoms.[23] To our knowledge, there are no data yet available examining the efficacy and tolerability of levetiracetam in the treatment of PTSD.

Levetiracetam is a novel anticonvulsant with a favorable side effect profile. Demonstration of the efficacy and safety of levetiracetam for patients with PTSD, including those refractory to standard anxiolytic treatments, will offer clinicians and their patients a valuable treatment strategy for this distressing and often disabling condition. This study therefore examined the efficacy, safety, and tolerability of levetiracetam in the treatment of PTSD.

METHOD

Retrospective analysis was undertaken of 23 patients receiving treatment for PTSD at the Anxiety Disorders Research Program outpatient clinic at the Cambridge Health Alliance, Cambridge, Mass., who, after being deemed partial or nonresponders to antidepressants, received therapy with levetiracetam in a naturalistic fashion. This study was approved by the Institutional Review Board of the Cambridge Health Alliance and was conducted in accordance with the Declaration of Helsinki.

Male and female patients between the ages of 18 and 75 years were eligible for study inclusion if they met DSM-IV diagnostic criteria for PTSD and had received at least 8 weeks of anxiolytic/antidepressant treatment. Additional inclusion criteria included a Hamilton Rating Scale for Depression (HAM-D)[24] score ≤ 21 and a Clinical Global Impressions-Severity of Illness scale (CGI-S)[25] score ≥ 4. Patients were excluded from the study if they were currently or previously diagnosed with bipolar disorder, schizophrenia, or other psychotic conditions.

Existing medication regimens were supplemented with a starting dose of 250 mg of levetiracetam at bedtime with a weekly dose escalation of 250 to 500 mg. The target dosage range was 1000 to 3000 mg/day in a twice daily or nightly regimen, based on each patient's individual response and tolerability to the added agent.

Changes in PTSD symptoms were evaluated using 5 measures. The primary outcome measure was the PTSD Checklist-Civilian Version (PCL-C),[26] a patient-rated questionnaire consisting of 17 items that assesses the impact of specific PTSD symptoms and encompasses 3 subscales that correspond to the 3 DSM-IV symptom clusters of PTSD. Secondary clinician-rated measures included the Hamilton Rating Scale for Anxiety (HAM-A),[27] HAM-D-17, CGI-S, and Clinical Global Impressions-Improvement scale (CGI-I).[25] The HAM-A is a 14-item instrument that assesses the severity of anxiety, the

Table 1. Clinical, Demographic, and Treatment Characteristics of Patients With PTSD Treated With Levetiracetam (N = 23)

Characteristic	Value
Gender, N (%)	
Male	9 (39)
Female	14 (61)
Age, mean ± SD (range), y	35.2 ± 9.8 (19–51)
No. previous medication trials, mean ± SD (range)	5.1 ± 2.0 (2–10)
Baseline levetiracetam dosage, mean ± SD (range), mg/d	1967 ± 650 (1000–3000)
Duration of treatment, mean ± SD (range), wk	9.7 ± 3.7 (4–20)
Comorbid condition, N (%)	
Depression	17 (74)
Obsessive-compulsive disorder	3 (13)
Generalized anxiety disorder	2 (9)
Panic disorder	2 (9)
Alcohol abuse	1 (4)
None	1 (4)

Abbreviation: PTSD = posttraumatic stress disorder.

Table 2. Concomitant Medications of Patients With PTSD Treated With Levetiracetam (N = 19)

Medication	No. of Patients
Sertraline	5
Clonazepam	5
Fluoxetine	4
Paroxetine	4
Citalopram	3
Quetiapine	3
Clonidine	2
Escitalopram	2
Lorazepam	2
Venlafaxine	1
Gabapentin	1
Bupropion	1

Abbreviation: PTSD = posttraumatic stress disorder.

HAM-D-17 is a 17-item scale that assesses the severity of depression, the CGI-S is a 1-item scale assessing the overall level of illness severity, and the CGI-I is a 1-item scale assessing the overall improvement compared to baseline.

Patient responder status at endpoint was defined as a statistically significant ($p < .05$) mean change in PCL-C scores and a CGI-I score ≤ 2 ("much improved" or "very much improved"). Patient remission status at endpoint was defined as a CGI-S score ≤ 2. In addition to the rating of clinical response, a subsequent chart review was conducted to assess the number of previous medication trials, the use and number of concomitant medications, and reports of adverse events.

Statistical analysis included descriptive statistics generated with Intercooled Stata 7.0 (2001) statistical software (Stata Corp., College Station, Tex.). Comparisons of baseline and endpoint mean differences in PCL-C, CGI-S, HAM-A, and HAM-D scores were performed using paired t tests.

Table 3. Score Change in 23 Patients With PTSD Treated With Levetiracetam

Scale	Baseline Score, mean ± SD	Endpoint Score, mean ± SD	Change
PCL-C	67.2 ± 9.4	43.7 ± 11.2	23.5*
CGI-S	6.0 ± 0.7	3.5 ± 1.3	2.5*
HAM-A	26.8 ± 4.9	13.3 ± 5.7	13.5*
HAM-D	10.6 ± 4.0	5.9 ± 4.5	4.7*

*$p < .001$ using paired t tests.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, PCL-C = PTSD Checklist-Civilian Version, PTSD = posttraumatic stress disorder.

Table 4. Adverse Events Reported by 23 Patients With PTSD Treated With Levetiracetam

Symptom	No. of Patients
Sedation	4
Tiredness	3
Light-headedness	1
Dry mouth	1
Dyspepsia	1
None	13

Abbreviation: PTSD = posttraumatic stress disorder.

RESULTS

Clinical and demographic characteristics of the sample are provided in Table 1. All but 4 patients (83%) were taking 1 or more concomitant medications (Table 2).

Patients were severely ill, with a mean ± SD baseline CGI-S score of 6.0 ± 0.7. Mean baseline and endpoint PCL-C, CGI-S, HAM-A, and HAM-D scores are shown in Table 3. The mean difference from baseline to endpoint was statistically significant across all measures ($p < .001$), with a decrease in PCL-C scores of 23.5, a decrease in CGI-S scores of 2.5, a decrease in HAM-A scores of 13.5, and a decrease in HAM-D scores of 4.7. All 3 PTSD symptom clusters on the PCL-C showed a response. The mean ± SD CGI-I score at endpoint was 2.3 ± 1.1. Thirteen patients (56%) met responder criteria at endpoint (PCL-C mean change = 23.5, CGI-I score ≤ 2), and 6 (26%) met remission criteria at endpoint (CGI-S score ≤ 2).

Levetiracetam at a mean ± SD dose of 1967 ± 650 mg/day for 9.7 ± 3.7 weeks was generally well tolerated. Adverse events were generally mild and are summarized in Table 4.

DISCUSSION

This study examined the efficacy, safety, and tolerability of the anticonvulsant agent levetiracetam in the treatment of refractory PTSD. Our findings suggest that add-on levetiracetam may be an effective therapeutic option for symptoms of PTSD. In our sample, patients were

severely ill prior to treatment with levetiracetam and had shown lack of response to multiple other conventional anxiolytic treatments. Levetiracetam significantly reduced anxiety, with patients showing a robust reduction from baseline on PCL-C, CGI-S, and HAM-A scores. Treatment with levetiracetam was well tolerated, with patients reporting generally mild side effects. No patients discontinued levetiracetam as a result of any of treatment-emergent side effects.

The favorable response to treatment with levetiracetam in this group of patients with PTSD adds to the growing body of literature supporting the use of anticonvulsants for the treatment of anxiety disorders, and in particular PTSD. It is also consistent with previous studies using levetiracetam in animal models of anxiety. However, our findings should be viewed with caution given the limited sample size and the open, uncontrolled, and retrospective design of the study.

These preliminary data suggest that levetiracetam may be an effective treatment in combination with antidepressant therapy for patients with PTSD who remain symptomatic after initial intervention. Further prospective and controlled studies are warranted to confirm these early findings.

Drug names: bupropion (Wellbutrin and others), citalopram (Celexa and others), clonazepam (Klonopin and others), clonidine (Catapres, Duraclon, and others), escitalopram (Lexapro), fluoxetine (Prozac and others), gabapentin (Neurontin and others), levetiracetam (Keppra), lamotrigine (Lamictal), lorazepam (Ativan and others), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), sertraline (Zoloft), tiagabine (Gabitril), topiramate (Topamax), venlafaxine (Effexor).

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