Levetiracetam as Adjunctive Therapy for Refractory Anxiety Disorders

Gustavo Kinrys, M.D.; John J. Worthington, M.D.; Lisa Wygant, B.A.; Fernanda Nery, B.A.; Hannah Reese, B.A.; and Mark H. Pollack, M.D.

Received Aug. 17, 2006; accepted Dec. 13, 2006. *From the Anxiety Disorders Research Program, Cambridge Health Alliance, Cambridge (Dr. Kinrys and Mss. Wygant and Nery); the Center for Anxiety and Traumatic Stress Disorders, Massachusetts General Hospital, Boston (Drs. Worthington and Pollack and Ms. Reese); and the Department of Psychiatry, Harvard Medical School, Boston (Drs. Kinrys, Worthington, and Pollack and Mss. Wygant and Nery), Mass.*

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Corresponding author and reprints: Gustavo Kinrys, M.D., Cambridge Health Alliance/Harvard Medical School, Department of Psychiatry, 1493 Cambridge St., Cambridge, MA 02139 (e-mail: gkinrys@challiance.org).

Background: Anxiety disorders are the most prevalent psychiatric disorders as a group, and despite the effectiveness of currently available treatments for anxiety, many patients (40%–65%) remain symptomatic after initial intervention. Thus, there is a significant need for efficacious pharmacologic agents that are safe and well tolerated and lead patients to remission of symptoms. We present a retrospective analysis that assessed the efficacy and tolerability of adjunctive levetiracetam, a novel anticonvulsant agent, in the treatment of refractory anxiety.

Method: Forty patients with DSM-IV anxiety disorders, who were deemed partial responders or nonresponders to anxiolytic therapy, received adjunctive levetiracetam in a naturalistic fashion during the time period from January 2004 through December 2004. We conducted a retrospective chart review. The primary outcome measures were the Clinical Global Impressions-Severity of Illness (CGI-S) scale and the Clinical Global Impressions-Improvement (CGI-I) scale. Mean change from baseline to endpoint was assessed using 2-tailed paired t tests.

Results: Levetiracetam at a mean ± SD dose of 1969 ± 819 mg/day for a mean ± SD time period of 9.3 ± 5.1 weeks was generally well tolerated. Patients were markedly ill with a mean ± SD baseline CGI-S score of 6.2 ± 0.6. Patients improved significantly, with an endpoint CGI-S score of 4.2 ± 1.8 ($p < .001$) and CGI-I score of 2.6 ± 1.2. Adverse events were generally mild, and only 4 patients discontinued levetiracetam because of side effects.

Conclusion: These preliminary data suggest that levetiracetam may be an effective adjunctive treatment for patients with anxiety disorders who remain symptomatic despite initial anxiolytic therapy.

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Anxiety disorders are the most prevalent psychiatric disorders as a group, with an estimated lifetime prevalence of nearly 25% in the general population.[1] As such, they represent a significant burden to society, especially with regard to their associated levels of psychosocial disability, somatic complications, and utilization of health care resources. Despite the effectiveness of currently available treatments for anxiety, many patients (40%–65%) remain symptomatic after initial intervention.[2] There remains a significant need for efficacious pharmacologic agents that are safe and well tolerated and lead patients to remission of symptoms.

An increasing body of evidence supports the potential efficacy of anticonvulsants for the treatment of anxiety disorders.[3–5] It has been suggested that chronically overactive output from the amygdala during the fear response could be responsible for the symptoms seen in anxiety disorders.[6] Anticonvulsants may help reduce the release of excitatory neurotransmitters in this circuit, thus correcting the abnormal patterns of neuronal activity and reducing the anxiety-related symptoms.[7]

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.[8,9] Recent evidence suggests that it may also exert its effects by modulating a function of the synaptic vesicle protein SV2A present only under pathophysiologic conditions.[10] In addition, animal data suggest that levetiracetam counteracts benzodiazepine withdrawal–induced anxiety in mice.[11] Its

potential antianxiety effects were also assessed in a preclinical study in which 54.5 mg of levetiracetam was administered intraperitoneally to rats.[11] The results showed significant reductions in anxiety-related behavior. Preclinical study results also showed a different anxiolytic profile as compared with classical benzodiazepines, suggesting a low risk for dependency and abuse potential.[12]

Levetiracetam has a favorable pharmacokinetic profile, with rapid absorption following oral administration, excellent bioavailability, rapid attainment of steady-state concentrations, linear kinetics, and minimal plasma protein binding.[13] In the treatment of epilepsy, it has shown minimal adverse effects and low propensity for drug interactions.[14,15] However, available data examining the efficacy and tolerability of levetiracetam in clinical studies of any psychiatric disorders remain limited. To our knowledge, only 2 studies have been published to date.[16,17] In these 2 open-label studies, 20 patients with social anxiety disorder and 23 patients with posttraumatic stress disorder, respectively, were treated with levetiracetam, yielding a robust response rate.

The study we present assessed the efficacy, safety, and tolerability of levetiracetam in the treatment of refractory anxiety disorders.

METHOD

We conducted a chart review and examined the first 40 patients with a primary diagnosis of a DSM-IV anxiety disorder who did not have a full response during their current episode despite an adequate dose and duration of their anxiolytic trial, defined as persistence of anxiety symptoms and a Clinical Global Impressions-Severity of Illness (CGI-S)[18] score ≥ 4, and who were treated with levetiracetam during the time period from January 2004 through December 2004. Subjects received levetiracetam as part of their clinical management at the outpatient clinic of the Anxiety Disorders Research Program, Cambridge Health Alliance, Cambridge, Mass., and at the Center for Anxiety and Traumatic Stress Disorders of Massachusetts General Hospital, Boston, Mass. This study was approved by our institutional review board and was conducted in accordance with the Declaration of Helsinki.

Male and female outpatients between the ages of 18 and 65 years were included in this study if they met DSM-IV diagnostic criteria for generalized anxiety disorder, panic disorder, social anxiety disorder, or posttraumatic stress disorder. Patients were excluded from the study if they were currently or previously diagnosed with bipolar disorder, substance abuse or dependence, schizophrenia, or other psychotic conditions.

Levetiracetam was added to the existing medication regimen at a starting dose of 250 mg/day. The dose was then increased depending on the individual response and tolerability, up to a maximum of 3000 mg/day. The primary outcome measures were the CGI-S and Clinical Global Impressions-Improvement (CGI-I)[18] scales. Patient responder status at endpoint was defined as a CGI-I score ≤ 2, and patient remission status at endpoint was defined as a CGI-S score ≤ 2. Clinical response was rated retrospectively at the date of the chart review. In addition to rating clinical response, a chart review was conducted to assess the number of previous medication trials, the use of concomitant medications, and reports of adverse events.

Statistical analysis included descriptive statistics generated by Stata software, version 8 (StataCorp, College Station, Tex.). Comparisons of endpoint with baseline CGI-S scores and analysis of change in CGI-I scores were performed using 2-tailed paired t tests.

Table 1. Clinical, Demographic, and Treatment Characteristics of Study Sample (N = 40)

Characteristic	Value
Gender, N (%)	
Male	29 (73)
Female	11 (28)
Age, mean ± SD (range), y	36.0 ± 10.0 (21–72)
No. of previous medication trials, mean ± SD (range)	5.3 ± 2.2 (2–10)
Levetiracetam dose, mean ± SD (range), mg/d	1969 ± 819 (250–3000)
Duration of treatment, mean ± SD (range), wk	9.3 ± 5.1 (2–24)
Primary diagnosis, N (%)	
Social anxiety disorder	15 (38)
Panic disorder	10 (25)
Generalized anxiety disorder	8 (20)
Posttraumatic stress disorder	7 (18)
Comorbid depression	17 (43)
Comorbid panic disorder	5 (13)
Comorbid generalized anxiety disorder	4 (10)
Comorbid obsessive-compulsive disorder	2 (5)
Comorbid attention-deficit/hyperactivity disorder	1 (3)

RESULTS

All of the 40 subjects that received at least 1 dose of levetiracetam returned to complete at least 1 follow-up assessment. Clinical and demographic characteristics of the sample are provided in Table 1. Concomitant medications are listed in Table 2.

Patients in this sample were severely ill with a mean ± SD baseline CGI-S score of 6.2 ± 0.6. Patients improved significantly with a mean endpoint CGI-S score of 4.2 ± 1.8 ($t = 2.0$, $df = 39$, $p < .001$) and CGI-I score of 2.6 ± 1.2. The mean change in CGI-S scores from baseline to endpoint was 2.0. Nineteen patients (48%) met responder criteria at endpoint, and 9 (23%) met remission criteria.

Levetiracetam at a mean ± SD dose of 1969 ± 819 mg/day for a mean ± SD time period of 9.3 ± 5.1 weeks

Table 2. Concomitant Medications of Study Sample (N = 40) at Baseline and for Duration of Study

Medication	Occurrences[a]
Clonazepam, lorazepam	5
Citalopram, paroxetine, fluoxetine, escitalopram, sertraline	5
Gabapentin, aripiprazole, quetiapine, bupropion, clonidine, venlafaxine	3

[a]Number of patients being treated with each medication. Some patients were receiving more than 1 concomitant medication.

Table 3. Adverse Events Reported by Study Sample (N = 40) During Adjunctive Treatment With Levetiracetam

Symptom	Occurrences[a]
Tiredness	9 (23)
Sedation	5 (13)
Dry mouth	3 (8)
Light-headedness	2 (5)
Diarrhea	2 (5)
None	21 (53)

[a]Data are shown as N (%) of study sample who reported each adverse event.

was generally well tolerated. Adverse events were generally mild and are summarized in Table 3. Twenty-one of the 40 patients (53%) reported having no adverse events. Four patients (10%) discontinued use of levetiracetam due to side effects, which included tiredness and/or sedation.

DISCUSSION

This study examined the efficacy, safety, and tolerability of the novel anticonvulsant agent levetiracetam in the treatment of anxiety disorders. Our findings suggest that adjunctive levetiracetam may be an effective therapeutic option for anxiety symptoms. Patients in this study were severely ill prior to treatment with levetiracetam and had previously shown resistance to conventional anxiolytic treatments. Adjunctive levetiracetam significantly reduced reported anxiety, with patients showing a noteworthy reduction from baseline in mean CGI-S scores. In the group of patients studied, the rate of response to augmentation with levetiracetam was encouraging, with 48% of patients meeting responder criteria (CGI-I score ≤ 2).

Treatment with levetiracetam appeared to be safe and well tolerated, with patients reporting generally mild side effects and 53% reporting virtually no side effects. Only 10% of patients discontinued treatment as a result of these side effects. Our findings are comparable in terms of response rates and consistent with previous reports supporting the efficacy of adjunctive anticonvulsants with purported anxiolytic properties and other agents in the treatment of refractory anxiety disorders.[17,19–22]

The significant response to levetiracetam of anxiety-related symptoms is consistent with the growing body of literature supporting the use of anticonvulsants for the treatment of anxiety disorders. It is also consistent with previous studies using levetiracetam in animal models of anxiety. However, these results should be interpreted with caution due to the open, uncontrolled, and retrospective design of the study.

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

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

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