Safety and Efficacy of Levetiracetam for Patients With Panic Disorder: Results of an Open-Label, Fixed-Flexible Dose Study

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Objective: To examine the safety and efficacy of the anticonvulsant levetiracetam in the treatment of patients with panic disorder.

Method: In an open-label, fixed-flexible dose study, 18 patients with panic disorder with or without agoraphobia (DSM-IV diagnostic criteria) were treated with levetiracetam for 12 weeks. Outcome was assessed with standard rating instruments (Clinical Global Impressions-Severity of Illness scale [CGI-S], Clinical Global Impressions-Improvement scale [CGI-I], and the 14-item Hamilton Rating Scale for Anxiety [HAM-A]) and by the number of panic attacks during the previous week. The study was conducted in 2 outpatient clinics in New York City from January 2004 through July 2005.

Results: Of the 13 patients completing the study, 11 were rated "very much" or "much" improved on the CGI-I. Panic attack frequency, anxiety (HAM-A), and global severity (CGI-S) ratings also demonstrated significant improvement (all $p < .00$). For most patients, clinical benefits were apparent after only 1 to 2 weeks of treatment. Levetiracetam was well tolerated with minimal side effects.

Conclusion: Given its favorable pharmacokinetics, side effect profile, and, if confirmed, early onset of action and efficacy, levetiracetam might represent significant progress in the pharmacologic management of panic disorder.

(J Clin Psychiatry 2006;67:1573–1576)

Received April 26, 2006; accepted Aug. 4, 2006. From Columbia University, New York State Psychiatric Institute, and Hillside Hospital, New York, N.Y.

This study was supported by UCB Pharma, Smyrna, Ga.

Poster presented at the 19th congress of the European College of Neuropsychopharmacology; September 16–20, 2006; Paris, France.

Dr. Papp reports no additional financial or other relationships relevant to the subject of this article.

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There are several classes of medications with established efficacy for panic disorder.[1] While response rates to pharmacotherapy approach 70%, medication side effects are substantial and the most frequently reported reasons for early treatment termination.[1] Comparable efficacy with reduced side effects is probably the single most important challenge in developing newer anxiolytic agents.

Panic disorder may have a pathophysiologic relationship with epilepsy,[2,3] but the evidence for directionality and causality remain tentative.[4] Stress-induced kindling has been suggested to play a significant role in the pathophysiology of epilepsy and panic disorder,[5] as well as posttraumatic stress disorder (PTSD).[6] Some speculate that the benefits of most anticonvulsants could be explained by their antikindling effects, but alternative or additional mechanisms of action (e.g., correcting of neurotransmitter abnormalities) have been suggested as well.[7] Anticonvulsants, such as valproate, carbamazepine, and clonazepam, have demonstrated preliminary evidence of efficacy in the treatment of panic disorder.[8–12]

Levetiracetam is an anticonvulsant, currently approved by the U.S. Food and Drug Administration for the adjunctive treatment of partial-onset seizures in patients with epilepsy. Preclinical evidence also supports the benefits of levetiracetam in kindled seizures[13] as well as its anxiolytic properties in animal models.[14,15]

A recent retrospective review[16] of 23 patients with refractory posttraumatic stress disorder found that levetiracetam, alone or in combination with antidepressant and other antianxiety medications, significantly improved the symptoms of severe PTSD. Levetiracetam was well tolerated with only mild side effects. Levetiracetam was also well tolerated by and effective for patients with social anxiety disorder treated in an open-label trial.[17]

The aim of the current study was to evaluate the efficacy and safety of levetiracetam for the treatment of patients with panic disorder.

METHOD

From January 2004 through July 2005, 18 English-speaking, medically healthy outpatients (11 men, 7 women), aged 18 through 63 years (mean = 43.8 ± 14.6

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years), with DSM-IV panic disorder (14 with and 4 without agoraphobia) were recruited through advertisements and referrals and enrolled in a 12-week, open-label, fixed-flexible dose study. After phone screen, initial evaluation, and consent process, patients signed an informed consent form. The study was conducted in 2 outpatient clinics (New York State Psychiatric Institute/Columbia University and Hillside Hospital, both in New York, N.Y.), and all procedures were approved by the respective institutional review boards.

The initial evaluation consisted of a psychiatric interview (confirmed by a semistructured interview[18]), rating scales (Clinical Global Impressions-Severity of Illness scale [CGI-S], Clinical Global Impressions-Improvement scale [CGI-I], the 14-item Hamilton Rating Scale for Anxiety [HAM-A], and agoraphobia, avoidance behavior scale [item B of the Panic and Agoraphobia Scale[19]] rated 0 = none to 4 = very frequent), number of panic attacks during the previous 4 weeks, medical history, physical exam, routine blood and urine toxicology tests, and electrocardiogram. Female patients of childbearing potential had to have a negative serum pregnancy test prior to study entry.

Those with current major depressive disorder, substance use disorder, or a history of bipolar disorder, psychosis, epilepsy, or suicidality were excluded. Eleven of the 18 patients had at least 1 comorbid condition (generalized anxiety disorder, N = 6; dysthymia, N = 6; social anxiety disorder, N = 6). Patients had to be free of psychiatric medications, including psychoactive herbal preparations, for at least 2 weeks (4 weeks for fluoxetine and monoamine oxidase inhibitors) prior to screening. As-needed benzodiazepines, not exceeding the equivalent of 0.5 mg alprazolam twice a week, until 10 days prior to the baseline visit were allowed.

Eligible patients were given a panic attack diary and were asked to return for the baseline visit 2 weeks later. They had to have had 4 panic attacks during the previous 4 weeks and at least 3 panic attacks between the screening and baseline visits in order to enroll. Presence or severity of agoraphobia was not an entry criterion. Severity of avoidance ranged from 0 (none) to 2 (occasional). At the baseline visit, exclusion/inclusion criteria were reevaluated, and those still eligible were started on medication.

Patients were instructed to take 250 mg of levetiracetam, morning and night with food (total of 500 mg/day). They were to continue to record panic attack frequency and medications taken daily. Patients were seen weekly for the first 4 weeks and then biweekly for 8 weeks, for a total of 8 visits over 12 weeks. A sufficient amount of medication was dispensed at each visit to last until the next appointment. At each visit, symptoms, side effects, and medication compliance (by pill count) were assessed. Blood pressure, pulse, and weight were also monitored. The dose of levetiracetam was increased weekly by a maximum of 500 mg/week up to the maximum daily dose of 2000 mg, depending on symptoms and side effects. In case of excessive daytime sedation, the total daily dose could be taken at night. Patients taking at least 125 mg twice a day for a minimum of 6 weeks were considered evaluable and were included in the "completer" analyses.

RESULTS

Thirteen of the 18 patients completed the study (as defined above). Of the 13 completers, 11 attended all 8 sessions, 1 stopped after visit 7 due to sedation, and 1 patient, a responder, did not return for follow-up after 6 weeks of treatment. Of the 5 noncompleters, 1 patient stopped due to persistent sedation, 1 due to irritability, and 1 for nonresponse. One patient was hospitalized for pre-existing lupus, and 1 patient, a responder at week 4, stopped due to unplanned pregnancy. All patients who took at least 1 dose of the study medication were included in the intent-to-treat (ITT) analyses, with the last observation carried forward.

Of the 13 completers, 4 were rated "very much improved" and 7 were rated "much improved" on the CGI-I, yielding a response rate of 85%. Including the 1 responder of the 5 noncompleters, the patient who had to stop at week 4 due to pregnancy, the ITT response rate was 67% (12/18). Clinical improvement in most responders was apparent after the first or second session. While not statistically significant, improved sleep, fewer panic attacks, and a mean decrease of 1 point on the CGI-S by the second week of treatment seemed to predict response at the final visit.

In the ITT analyses (using Student t tests), mean (± SD) pretreatment CGI-S scores decreased from 4.8 (± 0.4) to 3.0 (± 1.2) at the last observation ($t = 5.60$; $df = 16$; $p < .00$). Mean panic attack frequency dropped from 2.9 (± 0.7) at baseline to 1.5 (± 1.2), a highly significant change ($t = 4.6$; $df = 15$; $p < .00$). The mean baseline HAM-A score of 23.1 (± 5.3) also decreased significantly to 10.2 (± 7.7) ($t = 6.5$; $df = 16$; $p < .001$). There was no change on the agoraphobia, avoidance behavior scale.

For completers, improvement was also highly significant. Mean (± SD) CGI-S dropped from 4.8 (± 0.4) to 2.7 (± 1.1) ($t = 6.0$; $df = 12$; $p < .00$), panic attack frequency decreased from 2.9 (± 0.8) to 1.2 (± 1.2) ($t = 5.9$; $df = 12$; $p < .00$), and the mean HAM-A score dropped from 23.4 (± 5.6) to 7.6 (± 5.9) ($t = 8.9$; $df = 12$; $p < .00$). The mean daily dose of levetiracetam for completers during the last 2 weeks of the study was 1138 mg (± 627 mg; range: 306 mg to 2386 mg). The median daily dose during the same 2 weeks was 1071 mg (± 508 mg).

In general, side effects, if any, were mild, well tolerated, and usually resolved after the first 2 to 3 weeks. Side effects that were most likely attributable to the study drug included mild to moderate sedation (N = 7), headache

(N = 3), and irritability (N = 2), but were associated with study termination in only 2 patients (1 due to sedation and 1 due to irritability). On the other hand, 4 patients with insomnia reported significant improvement in sleep quality with no daytime sedation after the first week. Sedation seemed independent of dose and in most patients was successfully managed by switching the total dose to the evening. Mild, initial headaches responded to over-the-counter pain medications. One patient complained of slightly diminished libido and delayed orgasm. There were no changes in blood pressure, pulse, or weight.

DISCUSSION

In this small open-label study, treatment with the anticonvulsant levetiracetam resulted in significant improvement in patients with panic disorder with or without agoraphobia. Response rates to levetiracetam, 85% in completers and 67% in the intent-to-treat sample, compare very favorably to those reported for established antipanic medications, including the selective serotonin reuptake inhibitors (SSRIs). SSRIs are currently the first-line medication choice for panic disorder.[20]

At doses significantly lower than that indicated for epilepsy,[21] many patients reported clinically significant improvement as early as after the first or second week of treatment that was maintained through the duration of the study. Early onset of action, typically on the first day of levetiracetam treatment, was also observed in patients with refractory epilepsy.[22] Also consistent with the current findings, response to lower doses of certain antidepressant and other anxiolytic medications, compared with the effective doses recommended for other indications, has been reported in patients with panic disorder.[23,24]

Panic patients with insomnia experienced improved quality of sleep after the first few doses with no daytime sedation. When noted as a side effect, sedation was usually mild and transient. With the exception of 1 patient reporting mild, transient diminished libido, there was no evidence of weight gain or sexual dysfunction, the 2 most troublesome and most frequent side effects that significantly limit the utility of SSRIs.[25] That significant change in avoidance behavior lags behind general improvement and may not be detectable in studies of relatively short duration is an expected finding, particularly in panic patients with only mild agoraphobia.

The reported absence of significant withdrawal symptoms,[14] tolerance, and addiction potential[21] make levetiracetam a convenient alternative to benzodiazepines for patients with panic disorder and comorbid substance use disorder. Levetiracetam's unique pharmacologic properties,[26] also confirmed by extensive animal data,[14,15] may confer significant benefits for patients with special needs who also suffer from anxiety disorders; primary renal excretion, linear pharmacokinetics, cytochrome P450–independent metabolism, and virtually no drug-drug interactions are significant advantages for elderly patients,[27] for those with abnormal liver functions, and for the many patients requiring multidrug regimens for comorbid conditions.

In spite of its limitations—small sample size, open, uncontrolled design, focus on acute efficacy in a relatively short trial, and the exclusion of some comorbid conditions—this study demonstrates the potential benefits of levetiracetam in the treatment of patients with panic disorder. Given that side effects and delayed onset of action are the most significant limitations of the currently approved antipanic medications, the well-tolerated, possibly equally efficacious, and rapidly acting levetiracetam could present a significant advance in the pharmacologic management of panic disorder. Controlled trials with appropriate sample sizes are warranted.

Drug names: alprazolam (Xanax, Niravam, and others), carbamazepine (Carbatrol, Tegretol, and others), clonazepam (Klonopin and others), fluoxetine (Prozac and others), levetiracetam (Keppra).

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