Levetiracetam in Generalized Social Anxiety Disorder: A Double-Blind, Randomized Controlled Trial

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Objective: This multicenter, double-blind, placebo-controlled, 2-arm, parallel-group study was carried out to determine the effectiveness and safety of the novel anticonvulsant levetiracetam for the treatment of generalized social anxiety disorder (GSAD).

Method: After a 1-week, single-blind, placebo run-in period, 217 adult outpatients meeting *DSM-IV* criteria for social anxiety disorder, generalized type, were randomly assigned (1:1) to 12 weeks of double-blind treatment with either levetiracetam (n = 111) or placebo (n = 106). Participants were required to have scores of ≥ 60 on the Liebowitz Social Anxiety Scale (LSAS) and a total score of ≤ 17 on the 17-item Hamilton Depression Rating Scale (HDRS). The primary outcome measure was mean change from baseline on LSAS total score. Levetiracetam was initiated at 250 mg/d and flexibly titrated up to a maximum dose of 3,000 mg/d (1,500 mg bid). Dosage was held stable for the last 6 weeks of treatment. The study was conducted from September 2003 to June 2004.

Results: No statistically significant difference was found between the adjusted mean changes in LSAS score for levetiracetam (−24.4) and placebo (−28.7) using an efficacy intent-to-treat, last-observation-carried-forward analysis. Rates of response (≥ 30% reduction in LSAS score) were similar with 41.3% (levetiracetam) and 46.6% (placebo). No significant between-group differences were found on secondary outcome measures, which included changes in Sheehan Disability Scale, Clinical Global Impression of Change, and HDRS scores.

Conclusions: Although well-tolerated, levetiracetam failed to separate from placebo in this trial for the treatment of moderate to severe GSAD.

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With recent estimates of lifetime prevalence as high as 12.1%, social anxiety disorder (SAD) has been identified as one of the most common psychiatric conditions in the United States.[1] Social anxiety disorder has also been shown to be associated with significant distress, impairment, economic burden, and elevated rates of comorbid disorders, so it is critical to provide early intervention, with available data supporting efficacy for both psychotherapeutic and psychopharmacologic approaches. While a number of effective medications, such as the serotonin reuptake inhibitors or the monoamine oxidase inhibitors, have demonstrated efficacy for SAD, response rates in clinical trials of these agents are limited to 40%–70% for acute treatment.[2–4] Given these levels of nonresponse, it is important to develop novel agents for the treatment of SAD.

Pregabalin and gabapentin, each in 1 controlled study along with an open trial of topiramate, represent antiepileptic medications that have shown potential promise for the treatment of SAD.[5–7] These studies have led to investigations of alternate anticonvulsant agents, such as levetiracetam, also for this purpose.

Levetiracetam has been approved by the US Food and Drug Administration for adjunctive treatment of certain kinds of epilepsy.[8] It displays linear pharmacokinetics across the approved dose range and is rapidly absorbed. Levetiracetam is minimally protein bound, does not interact with the cytochrome P-450 system, and has few drug-drug interactions.[9] While the exact mechanism by which levetiracetam may exert anxiolytic effects is unclear, levetiracetam has been shown to bind specifically to a unique binding site—the synaptic vesicle protein 2A. These proteins are thought to increase the probability of release of secretory vesicles into the synapse, thereby enhancing appropriate neurotransmission.[10] This unique mechanism of levetiracetam is in contrast to the mechanisms of other anticonvulsant drugs.[11,12]

There is some preliminary clinical evidence to suggest potential efficacy of levetiracetam in the treatment of anxiety disorders. For example, a naturalistic study of 40 patients diagnosed with a *DSM-IV* anxiety disorder but with partial or nonresponse to standard treatment examined the effectiveness of adjunctive levetiracetam (250–3,000 mg daily).[13] Following a mean (SD) duration of 9.3 (5.1) weeks of treatment, 48% of subjects were deemed responders. Similarly, a

retrospective analysis of 23 patients with severe treatment-refractory posttraumatic stress disorder who were given a course of adjunctive levetiracetam along with their regular antidepressant reported significant improvements in all outcome measures, with 56% of patients eventually meeting responder criteria for the primary outcomes.[14] Both studies noted that levetiracetam was well tolerated. Levetiracetam has also been investigated as a monotherapy agent for panic disorder.[15] In this 12-week, open-label, flexible-dose study (N = 18), treatment with levetiracetam yielded a response rate of 67% in the intent-to-treat (ITT) population, with onset of clinical improvement evident even within the first 2 weeks. Again, the agent was well tolerated, with mild to moderate sedation the most frequently reported side effect.

Results from investigations of levetiracetam in SAD are mixed. Simon et al[16] conducted an 8-week, open-label, flexible-dose study (N = 20) of individuals with generalized SAD. Patients experienced significant improvement in social anxiety symptoms, with few reported side effects. Analysis of completers in this study showed significant symptom improvement as early as the second week. A small 7-week, randomized, double-blind, placebo-controlled study was subsequently carried out by Zhang et al.[17] In contrast to the other studies, no statistically significant differences were detected between placebo and levetiracetam treatment groups on primary outcome measures of social anxiety, although power was quite limited (N = 16). The authors noted a numerically greater reduction in social anxiety scores in the levetiracetam group and conducted a post hoc analysis that suggested that a larger trial of at least 62 patients per group might be sufficiently powered to demonstrate the efficacy of levetiracetam.

In order to resolve these conflicting findings and address some of the limitations raised by authors of these different trials, we conducted a well-powered 12-week, multicenter, randomized, double-blind, placebo-controlled, 2-arm, parallel-group study comparing levetiracetam and placebo as a treatment for SAD.

METHOD

This study was not registered with a clinical registry (eg, clinicaltrials.gov) as it was initiated in 2003, prior to the implementation of that requirement. From September 2003 to June 2004, 217 English-speaking, medically healthy outpatients, aged 18 to 70 years, with a clinically predominant diagnosis of *DSM-IV* social anxiety disorder, generalized subtype (GSAD), were recruited through advertisement and referral to be enrolled in this 12-week, randomized, double-blind, placebo-controlled study. The study was conducted in 20 centers across the United States with all procedures approved by the respective institutional review boards. All subjects were required to provide written informed consent after full explanation of the study and alternate treatment options.

Following the consent process, subjects were screened for study eligibility. The screening visit involved confirmation of GSAD diagnosis and evaluation of other psychiatric diagnoses with the Mini-International Neuropsychiatric Interview, a semistructured interview.[18] In addition, medical history, physical exam including vital signs, and routine blood and urine tests were also conducted for safety monitoring and to ensure participants did not suffer from clinically significant medical conditions. Subjects were also required to have a score of ≥ 60 on the Liebowitz Social Anxiety Scale (LSAS)[19] and a total score of ≤ 17 (with a score of ≤ 2 on the suicide subscale) on the 17-item Hamilton Depression Rating Scale (HDRS)[20] to be included in the study. Female patients of childbearing potential were required to have a negative serum pregnancy test at screening and negative urine pregnancy tests administered periodically throughout the study. Other exclusion criteria included the presence of another primary Axis I disorder (including *DSM-IV* diagnosis of another anxiety, eating, or substance use disorder in the prior 6 months), failure to respond to adequate trials of ≥ 2 medications to treat GSAD, and concomitant psychotropic medications in the previous week (fluoxetine in the previous 4 weeks).

At the end of the screening visit, eligible subjects underwent a single-blind, 1-week, placebo lead-in period. Those who maintained an LSAS score ≥ 60 and a Clinical Global Impression of Change[21] (CGI-C) > 2 (score range: 0–7) on their return visit (baseline—week 0) were then randomly assigned to double-blind treatment with either levetiracetam or matching placebo in a 1:1 ratio. Randomization was stratified according to LSAS scores at baseline (≤ 80, > 80) and age (≤ 40 years, > 40 years).

Study medication was titrated on a fixed schedule over the first 2 weeks from 250 mg/d up to 500 mg bid and then flexibly titrated over the next 4 weeks up to a maximum of 3,000 mg daily (1,500 mg bid). The dosage was then held stable for the remaining 6 weeks. Follow-up was weekly for 2 weeks and then at 2-week intervals until the end of the study (week 12).

The LSAS is a 24-item questionnaire assessing fear and avoidance of a range of social interactions and performance situations. All items are rated for both fear and avoidance, each scored on a scale of 0–3 (total score range: 0–144). The primary outcome for this study was change in total LSAS score from baseline to endpoint, with clinical response defined as ≥ 30% reduction of LSAS score from baseline and remission as an LSAS score ≤ 30 at the last evaluation visit attended. Secondary outcomes included CGI-C (response defined as final score of 1 or 2 [very much or much improved]) and changes in HDRS and Sheehan Disability Scale (SDS)[22] over time.

Statistical Analyses

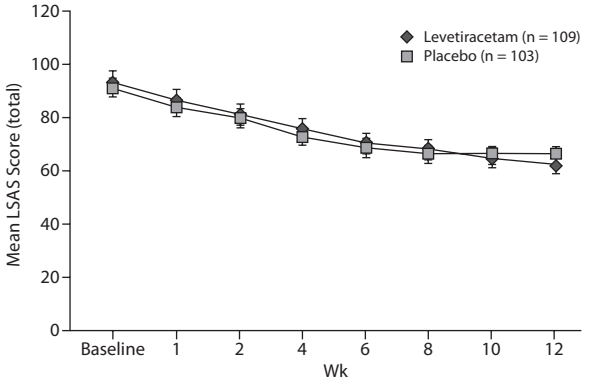
Sample size determination was based on detecting a 10-point mean treatment difference (estimated standard

Table 1. Demographic and Baseline Characteristics

Characteristic	Levetiracetam (n = 110)	Placebo (n = 106)
Men, n (%)	65 (59.1)	68 (64.2)
Age, mean ± SD, y	35.8 ± 11.6	35.8 ± 11.9
Age ≤ 40 years, n (%)	74 (67.3)	69 (65.1)
Age > 40 years, n (%)	36 (32.7)	37 (34.9)
Race, n (%)		
White	81 (73.6)	74 (69.8)
African American	16 (14.5)	15 (14.2)
Asian or Pacific Islander	1 (0.9)	4 (3.8)
Other	12 (10.9)	13 (12.3)
Age at illness onset, mean ± SD, y	14.1 ± 7.6	13.9 ± 8.4
Baseline LSAS score, mean ± SD	91.0 ± 18.1	93.2 ± 19.4
Baseline LSAS score ≤ 80, n (%)	29 (26.4)	32 (30.2)
Baseline LSAS score > 80, n (%)	81 (73.6)	74 (69.8)

Abbreviation: LSAS = Liebowitz Social Anxiety Scale.

Figure 1. Mean ± SE Total Liebowitz Social Anxiety Scale (LSAS) Scores During Double-Blind Treatment Period (last observation carried forward) With Levetiracetam and Placebo[a]



[a]No statistically significant differences were found between groups at any time point.

deviation [SD], 21.3) in the primary efficacy variable, change in total LSAS score. The presence of 95 evaluable patients in each treatment arm was calculated to provide 90% power for this difference, assuming a 2-sided, 2-sample independent group *t* test with a significance level of 5%. Assuming an attrition rate of 15%, we targeted a total of 224 patients for recruitment.

Analyses of results were performed for the efficacy ITT population (all randomized subjects who took any study medication and returned for ≥ 1 postbaseline evaluation) using the last observation carried forward (LOCF) as well as for observed cases completers analysis. Significance was examined using 2-sided hypothesis tests, with α = 5% for main effects and α = 10% for interaction effects. Changes in scores on primary outcome measure (LSAS) from baseline to last evaluation visit were compared using an analysis of covariance (ANCOVA), with treatment, pooled study center, and baseline LSAS scores in the model.

RESULTS

Of 265 patients who were screened, 217 (n = 133 men) entered the randomization phase, with 111 assigned to levetiracetam treatment and 106 subjects assigned to placebo treatment. Reasons for failure to enter the randomization phase included ineligibility (n = 29), withdrawal of consent for personal reasons not related to adverse events (n = 7), other reasons (n = 6), lost to follow-up (n = 3), and adverse events during placebo lead-in phase (n = 3). One subject dropped out of the levetiracetam group prior to medication intake and so is not included in the analyses. Lifetime comorbid psychiatric diagnoses included depression (n = 24), panic disorder (n = 5), alcohol abuse (n = 3), and generalized anxiety disorder (n = 2). The mean ± SD age at illness onset was 14.0 ± 8.0 years, with duration of illness of 21.8 ± 13.4 years. The mean ± SD LSAS scores at baseline of 91.0 ± 18.1 for the levetiracetam group and 93.2 ± 19.4 for the placebo group were similar and indicated a population with moderate to severe GSAD. No statistically significant differences were found in baseline demographics or other measured clinical characteristics between treatment groups (Table 1).

Overall, 148 of the 217 randomly assigned patients (n = 77 [70%], levetiracetam; n = 71 [67%], placebo) completed the treatment period, with no statistically significant difference in attrition rates for each group. There were no differences in demographic or clinical characteristics of subjects who terminated the study prematurely. Reasons for early termination included adverse events (n = 11, levetiracetam; n = 6, placebo), lack/loss of efficacy (n = 5, levetiracetam; n = 4, placebo), withdrawal of consent not related to adverse events/lack of efficacy (n = 5, levetiracetam; n = 1, placebo), and other reasons (n = 7, levetiracetam; n = 5, placebo). A further 24 subjects were lost to follow-up (n = 5, levetiracetam; n = 19, placebo).

The mean ± SD daily dose of levetiracetam was 1,180 ± 780 mg compared to 1,250 ± 760 mg of placebo. Side effects were generally in the mild to moderate range of severity, with no statistical differences found in the rates of treatment-emergent adverse effects experienced by the 2 treatment groups. The most commonly reported side effects included headache (20%, levetiracetam; 27%, placebo), fatigue (14%, levetiracetam; 13%, placebo), and somnolence (16%, levetiracetam; 9%, placebo).

In the ITT sample, no statistically significant differences were observed between treatment groups at any time point on the primary outcome (change in LSAS total score) (Figure 1) or on any of the subscales of this measure. Rates of treatment response (≥ 30% reduction in total LSAS score) in the ITT sample were similar in both groups (41.3%, levetiracetam; 46.6%, placebo), and rates of remission (LSAS score ≤ 30 at endpoint) were also comparable (13.8%, levetiracetam; 18.4%, placebo). Similar findings were obtained with subsequent analysis of the observed cases completers-

Table 2. Results Summary of Efficacy Intent-to-Treat Population Using Last Observation Carried Forward

	Levetiracetam (n = 109)				Placebo (n = 103)			
Outcome Measure	Endpoint, Mean ± SD	Mean Change From Baseline ± SE	Response Rate, %	Remission Rate, n (%)	Endpoint, Mean ± SD	Mean Change From Baseline ± SE	Response Rate, %	Remission Rate, n (%)
LSAS	65.7 ± 27.9	−24.4 ± 2.9[a]	41.3	15 (13.8)	62.4 ± 31.4	−28.7 ± 2.9[a]	46.6	19 (18.4)
HDRS	6.5 ± 5.4	0.1 ± 4.6	NA	NA	6.3 ± 5.9	0.1 ± 4.6	NA	NA
SDS	9.7 ± 7.6	−2.5 ± 8.2	NA	NA	9.0 ± 7.8	−2.6 ± 8.1	NA	NA
CGI-C	NA	NA	37.6	NA	NA	NA	38.8	NA

[a]Adjusted means.
Abbreviations: CGI-C = Clinical Global Impression of Change, HDRS = Hamilton Depression Rating Scale, LSAS = Liebowitz Social Anxiety Scale, NA = not applicable, SDS = Sheehan Disability Scale, SE = standard error.

only subgroup. Results from the ANCOVA model were not clinically significant, revealing an adjusted mean difference (levetiracetam – placebo) in LSAS change scores of 4.3 (95% CI, −3.5 to 12.1; $P = .282$). Additional analyses of the primary outcome were performed on subgroups within the ITT population to determine possible predictors of response. Clinically significant treatment effects for levetiracetam were not detected in any of the subgroups, which were characterized by age, gender, race, baseline LSAS score, duration of illness, or presence of comorbid depression.

Likewise, analysis of secondary outcomes (HDRS, CGI-C [response defined as score ≤ 2], and SDS) did not reveal any between-group differences, regardless of whether the ITT or observed cases completers-only subgroup was used (Table 2).

DISCUSSION

The results of this multicenter, randomized, double-blind, placebo-controlled clinical trial do not support levetiracetam as an efficacious monotherapy agent for SAD. While the mean decrease on the LSAS found with levetiracetam in this study was 25.4, which is comparable to the mean LSAS score changes found in other smaller studies of levetiracetam in SAD (ie, 20.5 and 28.7),[16,17] it was not significantly different from that seen in the placebo-treated patients in this trial. Additional comparison of LSAS subscale scores failed to distinguish between treatment arms, and levetiracetam also produced similar results to placebo on all secondary measures.

The findings from this large, randomized controlled trial do not confirm the previous positive results from an open, uncontrolled report,[16] but rather are consistent with the results from the earlier negative pilot placebo-controlled trial[17] examining the use of levetiracetam for SAD and provides evidence—across multiple outcome measures—that levetiracetam was not an effective monotherapy treatment of GSAD. While we cannot exclude the possibility that levetiracetam might be a helpful medication for particular patients (eg, perhaps those with a comorbid seizure disorder and SAD) or that it may have a role as an adjunctive therapy to more standard agents, this study does not support its routine use for the treatment of GSAD.

Although levetiracetam may not be an effective treatment for people with SAD, it was safe and reasonably well tolerated in this study. Given the initial reports of its efficacy as monotherapy and an augmenting agent for panic disorder and posttraumatic stress disorder, respectively, it may still hold promise as a treatment of these other anxiety disorders. Hopefully, the investigation of other novel agents will prove more fruitful for the treatment of SAD.

Drug names: fluoxetine (Prozac and others), gabapentin (Neurontin and others), levetiracetam (Keppra), pregabalin (Lyrica), topiramate (Topamax).

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REFERENCES

1. Kessler RC, Berglund P, Demler O, et al. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry.* 2005;62(6):593–602.
2. Allgulander C. Paroxetine in social anxiety disorder: a randomized placebo-controlled study. *Acta Psychiatr Scand.* 1999;100(3):193–198.
3. Stein MB, Fyer AJ, Davidson JR, et al. Fluvoxamine treatment of social phobia (social anxiety disorder): a double-blind, placebo-controlled study. *Am J Psychiatry.* 1999;156(5):756–760.
4. Blanco C, Raza MS, Schneier FR, et al. The evidence-based pharmacological treatment of social anxiety disorder. *Int J Neuropsychopharmacol.* 2003;6(4):427–442.
5. Pande AC, Davidson JR, Jefferson JW, et al. Treatment of social phobia with gabapentin: a placebo-controlled study. *J Clin Psychopharmacol.* 1999;19(4):341–348.
6. Pande AC, Feltner DE, Jefferson JW, et al. Efficacy of the novel anxiolytic pregabalin in social anxiety disorder: a placebo-controlled, multicenter study. *J Clin Psychopharmacol.* 2004;24(2):141–149.
7. Van Ameringen M, Mancini C, Pipe B, et al. An open trial of topiramate in the treatment of generalized social phobia. *J Clin Psychiatry.* 2004;65(12):1674–1678.
8. Farooq MU, Bhatt A, Majid A, et al. Levetiracetam for managing neurologic and psychiatric disorders. *Am J Health Syst Pharm.* 2009;66(6):541–561.
9. Radtke RA. Pharmacokinetics of levetiracetam. *Epilepsia.* 2001;42 (suppl 4):24–27.
10. Custer KL, Austin NS, Sullivan JM, et al. Synaptic vesicle protein 2 enhances release probability at quiescent synapses. *J Neurosci.* 2006;26(4):1303–1313.
11. Moroz G. High-potency benzodiazepines: recent clinical results. *J Clin Psychiatry.* 2004;65(suppl 5):13–18.
12. Kavoussi R. Pregabalin: from molecule to medicine. *Eur Neuropsychopharmacol.* 2006;16(suppl 2):S128–S133.
13. Kinrys G, Worthington JJ, Wygant L, et al. Levetiracetam as adjunctive therapy for refractory anxiety disorders. *J Clin Psychiatry.* 2007;68(7):1010–1013.
14. Kinrys G, Wygant LE, Pardo TB, et al. Levetiracetam for treatment-refractory posttraumatic stress disorder. *J Clin Psychiatry.* 2006;67(2):211–214.
15. Papp LA. Safety and efficacy of levetiracetam for patients with panic disorder: results of an open-label, fixed-flexible dose study. *J Clin Psychiatry.* 2006;67(10):1573–1576.
16. Simon NM, Worthington JJ, Doyle AC, et al. An open-label study of levetiracetam for the treatment of social anxiety disorder. *J Clin Psychiatry.* 2004;65(9):1219–1222.
17. Zhang W, Connor KM, Davidson JR. Levetiracetam in social phobia: a placebo controlled pilot study. *J Psychopharmacol.* 2005;19(5): 551–553.
18. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry.* 1998;59(suppl 20):22–33.
19. Heimberg RG, Horner KJ, Juster HR, et al. Psychometric properties of the Liebowitz Social Anxiety Scale. *Psychol Med.* 1999;29(1):199–212.
20. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry.* 1960;23:56–62.
21. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, MD: National Institute of Mental Health;1976:218–222.
22. Sheehan DV, Harnett-Sheehan K, Raj BA. The measurement of disability. *Int Clin Psychopharmacol.* 1996;11(suppl 3):89–95.