An Open-Label Study of Levetiracetam for the Treatment of Social Anxiety Disorder

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Objective: Social anxiety disorder is a disabling condition characterized by excessive fear and avoidance of social and performance situations. While a variety of effective pharmacotherapies exists, many patients do not fully respond to or tolerate available agents. Preclinical and early clinical experience with levetiracetam, a novel anticonvulsant agent, suggests that levetiracetam has anxiolytic properties and a favorable adverse event profile. Levetiracetam thus warrants systematic evaluation as a treatment option for anxiety disorders.

Method: Twenty adult outpatients who were recruited through advertisement and clinical referral and who met DSM-IV criteria for social anxiety disorder, generalized type, participated in this 8-week open-label, flexible-dose study from November 2002 to December 2003. Participants were required to have scores of ≥ 50 on the Liebowitz Social Anxiety Scale (LSAS) and ≥ 4 on the Clinical Global Impressions-Severity of Illness scale (CGI-S) at baseline. The presence of comorbid depression and anxiety disorders were permitted as long as social anxiety disorder was the primary disorder. Levetiracetam was initiated at 250 mg/day for the first week and flexibly titrated up to a maximum of 3000 mg/day (1500 mg b.i.d.). The primary outcome measure was change in the LSAS score at endpoint.

Results: There was a clinically significant 20.5-point decrease in LSAS scores in the intent-to-treat, last-observation-carried-forward analysis ($t = 3.1$; $p < .01$, $N = 20$). There were also significant reductions in CGI-S ($p < .01$) and Hamilton Rating Scale for Anxiety ($p < .02$) scores.

Conclusions: This pilot study supports the safety and potential efficacy of a novel agent, levetiracetam, for the treatment of social anxiety disorder. Larger controlled trials are warranted to confirm these results.

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Social anxiety disorder is a common psychiatric disorder with a lifetime prevalence of 13.3%,[1] making it the third most common psychiatric condition in the United States behind major depression and alcohol abuse. The emotional and social costs of social anxiety disorder are considerable, with increased associated physical and emotional health difficulties, alcohol and drug abuse, suicide attempts, poor marital and vocational functioning, financial dependence, use of general medical resources, and decreased educational attainment.[2–5] Despite first-line interventions such as selective serotonin reuptake inhibitors (SSRIs: e.g., sertraline, paroxetine), serotonin-norepinephrine reuptake inhibitors (SNRIs: e.g., venlafaxine), monoamine oxidase inhibitors (MAOIs: e.g., phenelzine), and cognitive-behavioral therapy (CBT) for social anxiety disorder, approximately 45% to 70% of patients fail to reach responder criteria after acute treatment, with an even greater proportion remaining at least somewhat symptomatic.[6–8] The purpose of this study was to examine the potential efficacy of a novel psychopharmacologic strategy, the use of levetiracetam, for the treatment of patients with social anxiety disorder.

Levetiracetam is a novel anticonvulsant agent with a generally favorable side effect profile and low propensity for drug interactions. An increasing body of research, recently reviewed by Shaywitz and Liebowitz,[9] supports the potential efficacy of a number of anticonvulsants for the treatment of anxiety disorders, including social phobia.[10–13] For example, there are double-blind data suggesting potential efficacy for gabapentin[10] and pregabalin[11] and open data with valproate[12] and topiramate.[13]

As discussed by Shaywitz and Liebowitz,[9] although the mechanism of action of antiepileptic agents in anxiety disorders remains unclear, most potentially effective agents from this class have activity in the GABA-ergic or glutamatergic systems. Levetiracetam reduces currents through high-voltage–activated calcium channels and has effects at a unique CNS binding site.[14,15] While the precise mechanism of action of levetiracetam remains to be elucidated, it does not have direct effects on GABA concentrations or GABA receptors; however, levetiracetam has been shown to promote chloride influx at the $GABA_A$ receptor by inhibiting the $GABA_A$ receptor modulators zinc and β-carbolines, an action shared with clonazepam and valproate.[16] Recent animal data suggest that levetiracetam counteracts benzodiazepine withdrawal–induced anxiety in mice.[17]

Although more definitive research is needed, it is possible that modulation of GABA-ergic effects may underlie the anxiolysis observed in this group of patients with social anxiety disorder. Moreover, clinical experience with levetiracetam suggests its anxiolytic effects as well[32] and warrants further systematic study. Demonstration of the safety and efficacy of levetiracetam for patients with social anxiety disorder will offer clinicians and their patients a valuable treatment strategy for this distressing, and often disabling, condition.

METHOD

Twenty adult outpatients were recruited through advertisement and clinical referral for participation in an 8-week open-label, flexible-dose study of levetiracetam for DSM-IV social anxiety disorder, generalized type. Participants were diagnosed by a study psychiatrist using the Structured Clinical Interview for DSM-IV (SCID).[18] The presence of comorbid depression and anxiety disorders were permitted as long as social anxiety disorder was the primary disorder. Other inclusion criteria included a Liebowitz Social Anxiety Scale (LSAS)[19] rating of ≥ 50, a Clinical Global Impressions-Severity of Illness scale (CGI-S)[20] score of ≥ 4, and a 17-item Hamilton Rating Scale for Depression (HAM-D)[21] score of ≤ 21.

Exclusion criteria included comorbid current or past bipolar disorder, schizophrenia, or other psychotic conditions; a history of alcohol or substance abuse or dependence within the last 6 months; or a positive toxicology screen consistent with alcohol or substance abuse at baseline. Pregnant women and patients with significant unstable medical illness or ongoing psychotherapy directed toward the treatment of social anxiety disorder were also excluded. All patients gave informed consent, and the study was approved by the Institutional Review Board at Massachusetts General Hospital.

Table 1. Paired t Test for LSAS, HAM-A, HAM-D, CGI-S, Q-LES-Q, and SDS Scores at Baseline and Study Endpoint (last visit carried forward)

Test	N	Baseline Mean (SD)	Endpoint Mean (SD)	t	Significance p ≤	Effect Size (Cohen's d)
LSAS	20	90.8 (19.2)	70.4 (37.1)	3.1	.01	0.69
HAM-A	15	18.7 (8.8)	13.3 (7.9)	2.5	.02	0.65
HAM-D	15	9.7 (4.3)	8.2 (6.5)	1.2	.26	0.27
CGI-S	20	6.0 (1.0)	4.7 (1.2)	3.3	.01	1.17
Q-LES-Q	13	52.0 (4.7)	57.2 (11.8)	–1.9	.08	0.58
SDS total	13	15.9 (4.1)	10.7 (7.2)	2.0	.07	0.89
Work	13	3.9 (2.6)	3.2 (2.6)	0.6	.55	0.27
Social	13	7.3 (1.4)	4.7 (2.4)	3.5	.04	1.32
Family	13	3.8 (2.0)	2.8 (2.7)	1.4	.18	0.42

Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, LSAS = Liebowitz Social Anxiety Scale, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire, SDS = Sheehan Disability Scale.

Levetiracetam was initiated at 250 mg/day for the first week and flexibly titrated up to a maximum of 3000 mg/day (1500 mg b.i.d.) over the next 7 weeks. Participants were seen weekly for the first 2 weeks of the study and then at 2-week intervals for the remainder of the trial. Significance was examined with 2-tailed paired t tests for both the intent-to-treat, last-observation-carried-forward analyses and for the observed-cases completers analysis of the primary outcome measure, the LSAS. Secondary measures included the Hamilton Rating Scale for Anxiety (HAM-A),[22] Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q),[23] and Sheehan Disability Scale (SDS).[24]

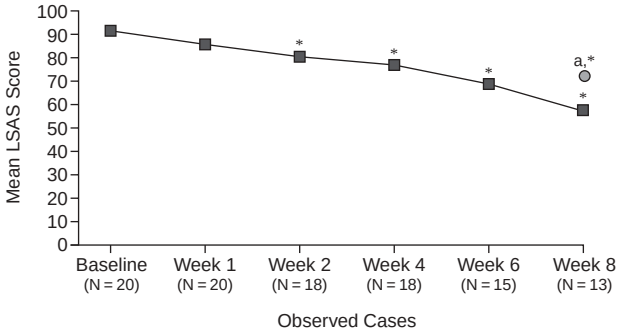
RESULTS

The study population comprised 20 patients (16 male/4 female; mean ± SD age 35.6 ± 12.8 years) who participated in the 8-week trial. Participants had a high level of symptoms at baseline, with a mean (SD) CGI-S score of 6.0 (± 1.0; severe) and a mean (SD) LSAS score of 90.8 (± 19.2) (Table 1). The cohort had a mean ± SD duration of illness of 35.6 (± 13.0) years and a mean ± SD age at onset of 10.3 (± 4.2) years. Six patients reported a history of prior trials of SSRIs or venlafaxine alone or in combination with benzodiazepines, which had been discontinued due to side effects or lack of efficacy.

Fifty percent of the sample (10/20) met DSM-IV criteria for 1 current comorbid Axis I disorder: 6 patients (30%) had generalized anxiety disorder (GAD), and 4 patients (20%) had major depressive or dysthymic disorder as diagnosed by the SCID. Five additional patients reported a past episode of major depression, and 3 had a prior history of alcohol abuse.

The mean ± SD endpoint dose of levetiracetam was 2013 ± 947.5 mg/day (range, 500–3000 mg/d), with a mean ± SD dose of 2423 ± 786.5 mg/day (range, 500–3000) for study completers. Sixty-five percent (13/20) of

Figure 1. Week-by-Week Mean Liebowitz Social Anxiety Scale Score (observed cases)



[a]Mean endpoint LSAS score for all patients.
*p < .01 difference from baseline LSAS score.

participants completed the 8-week trial. Three patients discontinued due to side effects (drowsiness and nervousness), 1 discontinued due to lack of efficacy, and 3 were lost to follow-up. Levetiracetam was well tolerated, with generally mild and transient side effects including fatigue (2/20), sedation (6/20), headache (2/20), restlessness (2/20), nausea (2/20), and dry mouth (2/20).

There was a clinically significant 20.5-point decrease in the primary outcome measure, the LSAS, at endpoint in the intent-to-treat, last-observation-carried-forward analysis ($t = 3.1$; $p < .01$; Table 1). There was also significant symptom reduction as assessed by the CGI-S and the HAM-A. There was a trend toward significant improvement in quality of life as measured by the Q-LES-Q and SDS. In the completers analysis, a significant improvement on the LSAS was evident by week 2, and this improvement persisted through the end of the trial (Figure 1).

DISCUSSION

This open, prospective study provides suggestive evidence that levetiracetam may be a safe and effective treatment option for patients with generalized social anxiety disorder. Although SSRI or SNRI antidepressants remain first-line interventions for social anxiety disorder,[25] there are a number of disadvantages associated with their use, including side effects such as sexual dysfunction, a fairly long latency of effect, and a risk of inducing manic episodes in patients with comorbid depression who are at risk for bipolar disorder. In addition, many patients who tolerate these agents either do not respond to them or have a limited response.

While benzodiazepines are alternative agents effective for social anxiety disorder,[26] the high rates of comorbid alcohol abuse disorders seen with social anxiety disorder,[3] concerns about the potential risk of physiologic and psychological dependence, and sedation, as well as cognitive impairment in the elderly[27] with chronic benzodiazepine administration, limit their use of benzodiazepines. In contrast, levetiracetam appears to be well tolerated in young and elderly patients with neurologic (e.g., epilepsy, cognitive) or anxiety disorders.[28] Thus, levetiracetam, a generally well-tolerated agent from the anticonvulsant class without abuse liability or potential for significant drug-drug interactions, may have a valuable role in the treatment of social anxiety disorder, either as a primary agent or, potentially, though unstudied at present, as an adjunctive agent for refractory patients.

Although of possible interest for use in bipolar disorder,[29] levetiracetam's antidepressant effects remain unknown at present, and it thus may not be appropriate as monotherapy for patients with significant comorbid depression. In our study, the reductions in CGI-S and LSAS scores with treatment do not appear to be explained by the presence of response to a comorbid disorder, as the amount of reduction was lower in the presence of comorbidity (1.4 vs. 1.0, $t = 2.2$, $p = .04$ for CGI-S and 31 vs. 9.5, $t = 1.8$, $p = .09$ for LSAS).

The open nature of this trial and the small sample of patients with social anxiety disorder examined to date with levetiracetam make it premature to draw definitive conclusions regarding its effectiveness or lack of efficacy. In addition, the 8-week duration of this trial was likely too short to see the full effect of levetiracetam on social anxiety disorder symptoms; for example, a study of the SSRI sertraline demonstrated continued improvement in LSAS scores through 20 weeks of treatment,[30] and another study of responders to a 12-week trial of paroxetine showed continued gains in the following 24 weeks.[31] Our study thus likely underestimates the potential effect of levetiracetam on final social anxiety disorder severity, which may in part explain the relatively high mean LSAS at endpoint, despite a clinically significant reduction of 20 points. However, given its generally favorable side effect profile and tolerability and the ongoing unmet need for additional effective pharmacotherapy options for the treatment of social anxiety disorder, systematic evaluation of levetiracetam in a longer, adequately powered randomized controlled study in social anxiety disorder is warranted.

Drug names: clonazepam (Klonopin and others), gabapentin (Neurontin and others), levetiracetam (Keppra), paroxetine (Paxil and others), phenelzine (Nardil), sertraline (Zoloft), topiramate (Topamax), venlafaxine (Effexor).

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