Tiagabine for the Treatment of Generalized Anxiety Disorder: A Randomized, Open-Label, Clinical Trial With Paroxetine as a Positive Control

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Background: Gamma-aminobutyric acid (GABA) plays a central role in the pathophysiology of anxiety. Tiagabine, a selective GABA reuptake inhibitor, enhances normal GABA tone. This 10-week, randomized, open-label trial evaluated tiagabine in patients with generalized anxiety disorder (GAD), with paroxetine serving as a positive control.

Method: Adult patients with DSM-IV GAD were randomly assigned to receive either tiagabine or paroxetine. Tiagabine was initiated at 4 mg/day (2 mg morning and evening) during week 1. Between weeks 2 and 6, the dose was individually titrated in 2-mg increments (maximum increase of 4 mg/week) for optimal response to a maximum dose of 16 mg/day (8 mg morning and evening). During weeks 7 through 10, patients received the dosage determined during the titration period. Paroxetine was initiated at 20 mg nightly for the first week and similarly titrated in 10-mg increments to a maximum dose of 60 mg/day. Assessments included the Hamilton Rating Scale for Anxiety (HAM-A), Hospital Anxiety and Depression Scale (HADS), Hamilton Rating Scale for Depression (HAM-D), Pittsburgh Sleep Quality Index (PSQI), and Sheehan Disability Scale (SDS).

Results: Forty patients were enrolled (tiagabine, N = 20; paroxetine, N = 20). Mean final doses were tiagabine 10 mg/day (range, 4–16 mg/day) or paroxetine 27 mg/day (range, 20–40 mg/day). Tiagabine and paroxetine significantly reduced anxiety (HAM-A and HADS total and anxiety subscales). Although patients were not diagnosed with a mood disorder, both tiagabine and paroxetine reduced comorbid depressive symptoms (HAM-D total and HADS total and depressive subscale). Tiagabine and paroxetine significantly improved sleep quality (PSQI) and functioning (SDS). Both tiagabine and paroxetine were well tolerated.

Conclusion: The selective GABA reuptake inhibitor tiagabine and the positive control paroxetine significantly reduced anxiety and comorbid depressive symptoms, improved sleep quality and functioning, and were well tolerated in patients with GAD. Tiagabine may be a therapeutic option for the treatment of anxiety disorders.

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Generalized anxiety disorder (GAD) is a chronic and disabling disorder, characterized by uncontrollable worrying and somatic anxiety (hypervigilance, fatigue, sleep disturbances). GAD has a lifetime prevalence in the United States of approximately 5%,[1,2] and is known to have high comorbidity rates with other psychiatric disorders, including depression,[1] and sleep disturbances/disorders, such as insomnia.[3] Despite the availability of effective pharmacotherapies for the treatment of GAD, such treatments have been associated with tolerability issues, abuse, and high relapse/low remission rates, creating the need for additional therapeutic options.[4,5]

The γ-aminobutyric acid (GABA) system is involved in a variety of disorders and plays a central role in the pathophysiology of anxiety.[6,7] Historically, it was the clinical efficacy of the benzodiazepines (allosteric modulators of the $GABA_A$ receptor) that indicated an involvement of the GABA system in anxiety.[6] More recently, neuroimaging studies of patients with anxiety disorders, including GAD, have found deficiencies in the GABA system in the form of either reduced GABA receptor sensitivity/density or deficit of endogenous GABA.[8–12]

Tiagabine is a selective GABA reuptake inhibitor that increases synaptic GABA availability by blocking the reuptake of GABA via inhibition of the GABA transporter.[13,14] In preliminary reports, tiagabine has shown promise as monotherapy or augmentation therapy for anxiety, including GAD, posttraumatic stress disorder, and panic disorder.[15–18] Furthermore, tiagabine has been shown to improve sleep parameters in elderly volunteers.[19]

This trial evaluated tiagabine for the treatment of GAD. A positive control group of patients treated with paroxetine, commonly used for the treatment of GAD, was included to assess the sensitivity of the study design.

METHOD

This was a 10-week, randomized, open-label, positive-controlled, blinded-rater trial of outpatients with GAD. The trial was conducted in 3 affiliated health care sites, from May 2002 through November 2002, using a protocol approved by individual institutional review boards at each site.

Patient Selection

Male and female outpatients between the ages of 18 and 65 years were eligible for trial inclusion if they met DSM-IV diagnostic criteria for GAD using the Mini-International Neuropsychiatric Interview.[20] Inclusion criteria included a Hamilton Rating Scale for Anxiety (HAM-A)[21] score ≥ 18 and rating of at least "moderately ill" on the Clinical Global Impressions-Severity (CGI-S) scale.[22] Patients were also required to have a score on the Covi Anxiety Scale[23] greater than the total score on the Raskin Depression Scale[24] to ensure they did not have significant comorbid depression.

Patients were excluded from the trial if they were diagnosed with any other Axis I psychiatric disorder, had a baseline score ≥ 15 on the Hamilton Rating Scale for Depression (HAM-D),[25] or had a total score > 9 or a score > 3 on any 1 item of the Raskin Depression Scale. Other exclusion criteria included previous treatment with tiagabine, concomitant pharmacologic treatment for GAD, or history of drug/alcohol abuse. Patients provided informed consent.

Study Design

Following a 14- to 28-day washout period for prior anxiolytic medications, patients were randomly assigned to receive tiagabine or paroxetine, a selective serotonin reuptake inhibitor (SSRI). Tiagabine (taken with food) was initiated at 4 mg/day (2 mg morning and evening) for the first week and then individually titrated in 2-mg increments, with a maximum increase of 4 mg/week, for optimal response (efficacy/tolerability) between weeks 2 and 6. During weeks 7 through 10, patients received the dosage determined during the titration period. The maximum tiagabine dose was not to exceed 16 mg/day (8 mg morning and evening). Paroxetine was initiated at 20 mg nightly for the first week and similarly titrated in 10-mg increments. The maximum paroxetine dose was not to exceed 60 mg/day. Patients were tapered off study drug between poststudy weeks 11 and 13.

Assessments

Assessments included the HAM-A, Hospital Anxiety and Depression Scale (HADS),[26] HAM-D, and Clinical Global Impressions of Change (CGI-C).[22] Sleep quality was evaluated using the Pittsburgh Sleep Quality Index (PSQI), a patient-rated, 19-item, 7-component questionnaire.[27] Individual component scores range from 0 (no difficulty) to 3 (severe difficulty); the global score, a summation of all 7 components, ranges from 0 to 21, with a score > 5 being suggestive of significant sleep disturbance. Functioning was assessed using the Sheehan Disability Scale (SDS).[28] The SDS is a patient-rated, simple, 3-item questionnaire employing an 11-point visual analog scale, where 0 represents no impairment and 10 indicates highly impaired. A score ≥ 5 on any of the 3 items represents significant functional impairment. The evaluation of tolerability was based on documented adverse events, physical examinations, and sexual functioning as assessed using the Derogatis Interview for Sexual Functioning: Male/Female (DISF).[29] The DISF is a patient-rated, gender-keyed, 25-item, 5-domain questionnaire designed to measure sexual functioning, where lower scores represent sexual impairment.

Statistical Analysis

Randomized patients with at least 1 postbaseline efficacy measurement were evaluated for efficacy using the last-observation-carried-forward analysis. All patients who received at least 1 dose of study medication (intent-to-treat population) were evaluated for tolerability. Comparisons to baseline in HAM-A, HADS, HAM-D, PSQI, SDS, and DISF were performed using a paired t test. Additionally, scores on the HAM-A psychic and somatic anxiety subscales and HADS anxiety and depression subscales were also analyzed using a similar approach. CGI-C data were analyzed using the Cochran-Mantel-Haenszel test adjusted for sites.

Degree of response was assessed based on previously published criteria. A reduction of ≥ 30% in HAM-A total score is considered meaningful improvement in functional status.[28,30] Meaningful improvement that occurs within weeks 1 or 2 and is maintained to endpoint is considered sustained onset.[31] Reduction of ≥ 50% in HAM-A total score at endpoint is defined as treatment response. A HAM-A total score of ≤ 7 at endpoint is defined as remission.[32] Because of the nature of the study design and the small sample size, no comparative statistical analyses were reported.

RESULTS

Forty patients were enrolled (tiagabine, N = 20; paroxetine, N = 20). Demographics and baseline clinical characteristics were similar between treatment groups (Tables 1 and 2). All 40 patients received study medication and were evaluable for efficacy. Fourteen patients in the tiagabine treatment group and 16 patients in the paroxetine treatment group completed the trial. Reasons for discontinuation were adverse events (tiagabine, N = 1; paroxetine, N = 2) and other (tiagabine, N = 5; paroxetine, N = 2). No patients discontinued due to lack of efficacy.

Table 1. Demographic and Baseline Clinical Characteristics

Characteristic[a]	Tiagabine (N = 20)	Paroxetine (N = 20)
Age, y (range)	32 (19–50)	38 (20–60)
Sex, N (%)		
Male	8 (40)	9 (45)
Female	12 (60)	11 (55)
Weight, kg	80.3 (5.4)	72.7 (3.9)
Age at onset of GAD, y	31 (2.1)	35 (2.5)
Duration of GAD,[b] y	1.2 (0.55)	2.3 (0.80)
CGI-S, N (%)		
Moderately ill	12 (60)	16 (80)
Markedly ill	8 (40)	4 (20)

[a]Values shown as mean (SEM) unless otherwise specified.
[b]Although patients were newly diagnosed with GAD, they had had long-standing symptoms of anxiety.
Abbreviations: CGI-S = Clinical Global Impressions-Severity, GAD = generalized anxiety disorder.

Table 2. Mean (SEM) Scores on Assessment Scales for Adult Patients With Generalized Anxiety Disorder

	Tiagabine (N = 20)		Paroxetine (N = 20)	
Scale	Baseline	Week 10	Baseline	Week 10
HAM-A total	24.4 (0.87)	13.8 (1.9)*	22.4 (1.2)	10.6 (1.3)*
Psychic anxiety subscale	13.8 (0.69)	7.8 (1.0)*	12.6 (0.63)	6.3 (0.81)*
Somatic anxiety subscale	10.6 (0.53)	6.0 (1.0)*	9.8 (0.70)	4.4 (0.60)*
HADS total	23.6 (1.2)	15.6 (1.9)*	20.7 (1.3)	11.6 (1.6)*
Anxiety subscale	15.3 (0.61)	9.8 (1.1)*	13.6 (0.63)	8.0 (1.0)*
Depression subscale	8.3 (0.82)	5.8 (0.99)*	7.2 (0.85)	3.6 (0.72)*
HAM-D total	13.1 (0.44)	9.2 (1.1)*	12.4 (0.77)	8.3 (0.89)*
PSQI global	11.5 (0.73)	6.3 (0.75)*	10.2 (0.86)	7.0 (0.77)*
SDS total	15.2 (1.9)	7.7 (1.7)*	13.0 (2.2)	5.2 (1.4)*
Work	4.9 (0.82)	2.4 (0.51)*	3.6 (0.82)	1.4 (0.37)*
Social life	5.2 (0.64)	3.2 (0.62)*	5.2 (0.62)	2.5 (0.49)*
Family life	5.7 (0.64)	3.0 (0.57)*	4.7 (0.58)	1.8 (0.34)*
DISF[a]				
Male	74.6 (9.2)	73.7 (11.2)	72.0 (12.0)	63.8 (8.6)
Female	37.1 (10.2)	57.7 (11.3)*	49.7 (6.8)	43.0 (7.7)

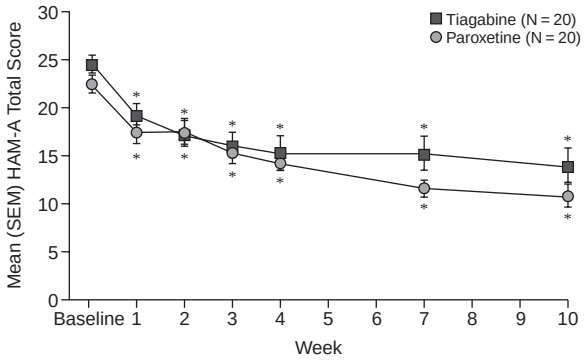
[a]For male, tiagabine (N = 8) and paroxetine (N = 9); for female, tiagabine (N = 12) and paroxetine (N = 11).
*p < .05 relative to baseline.
Abbreviations: DISF = Derogatis Interview for Sexual Functioning, HADS = Hospital Anxiety and Depression Scale, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, PSQI = Pittsburgh Sleep Quality Index, SDS = Sheehan Disability Scale.

The mean final dosage was approximately 10 mg/day (range, 4–16 mg/day) for tiagabine and approximately 27 mg/day (range, 20–40 mg/day) for paroxetine.

Efficacy

Tiagabine and paroxetine significantly reduced anxiety, as shown by significant reductions from baseline in mean scores on the clinician-rated HAM-A total (Figure 1) and psychic and somatic anxiety subscales and patient-rated HADS total and anxiety subscale (Table 2). The percentage of patients rated as treatment responders

Figure 1. Mean Total Scores on the Hamilton Rating Scale for Anxiety (HAM-A) for Patients With Generalized Anxiety Disorder Treated With Tiagabine or Paroxetine



*p < .05 relative to baseline.

(a ≥ 50% reduction in HAM-A total score at endpoint) was 40% (N = 8) for patients receiving tiagabine and 60% (N = 12) for those receiving paroxetine. Sustained onset (reduction of ≥ 30% in HAM-A total score within the first 2 weeks of treatment that was maintained to endpoint) was achieved in 30% (N = 6) of the tiagabine treatment group and 15% (N = 3) of the paroxetine treatment group. The percentage of patients who achieved remission (HAM-A total score of ≤ 7 at endpoint) was 20% (N = 4) for both treatment groups.

Although patients were not diagnosed with a mood disorder, both tiagabine and paroxetine reduced comorbid depressive symptoms, as shown by significant reductions in mean HAM-D total score and HADS depression subscale from baseline (Table 2). Moreover, tiagabine and paroxetine significantly improved sleep quality. Significant reductions from baseline in the mean PSQI global score were observed (Table 2). Eighty-five percent of patients treated with paroxetine (N = 17) had a positive clinical response (much or very much improved on the CGI-C) at endpoint compared with 60% of patients treated with tiagabine (N = 12). Tiagabine and paroxetine significantly improved patients' functioning, as assessed by the SDS (Table 2).

Tolerability

Both tiagabine and paroxetine were well tolerated. The 4 most commonly reported adverse events were headache, nausea, anorexia, and dizziness for patients receiving tiagabine and headache, dry mouth, insomnia, and nausea for patients receiving paroxetine (Table 3). Four patients receiving paroxetine reported sexual dysfunction (i.e., increased libido [N = 1], decreased libido [N = 2], abnormal ejaculation [N = 1], anorgasmia [N = 1], and abnormal sexual functioning [N = 1]). Tiagabine significantly improved female sexual functioning compared

Table 3. Most Common Treatment-Emergent Adverse Events (> 10%) in Adults With Generalized Anxiety Disorder

	Tiagabine (N = 20)		Paroxetine (N = 20)	
Adverse Event	N	%	N	%
Headache	11	55	8	40
Nausea	7	35	4	20
Anorexia	6	30	2	10
Dizziness	6	30	0	0
Somnolence	5	25	3	15
Diarrhea	4	20	0	0
Dry mouth	3	15	5	25
Increased appetite	3	15	0	0
Vasodilatation	3	15	0	0
Vomiting	3	15	0	0
Insomnia	1	5	4	20

with baseline, as assessed by the DISF at endpoint (Table 2). Changes in sexual functioning were not observed in men receiving tiagabine. Paroxetine reduced sexual functioning versus baseline in both men and women, although the differences did not reach statistical significance.

Most adverse events were mild to moderate in nature, and no serious adverse events were reported for either tiagabine or paroxetine. No substantial effects on vital signs or body weight were observed for tiagabine or paroxetine. One patient receiving tiagabine discontinued due to headache, blurred vision, and dizziness. Two patients receiving paroxetine withdrew, with one due to sharp chest pain and the other due to sedation, headache, palpitations, tension, and twitching.

DISCUSSION

This clinical trial evaluated the selective GABA reuptake inhibitor tiagabine for the treatment of GAD and provides an important account of anxiolytic response of tiagabine and its effect on mood, sleep, and functioning in a psychiatric population. The results showed that tiagabine (mean dose = 10 mg/day, divided between morning and evening), as well as the positive-control paroxetine (mean dose = 27 mg nightly), significantly reduced anxiety and comorbid depressive symptoms and improved sleep quality, overall clinical condition, and functioning. Both tiagabine and paroxetine were well tolerated, with few patients discontinuing due to adverse events and no reports of serious adverse events. The observed adverse events were consistent with known tolerability profiles.[33,34]

In the current trial, a positive control group of patients treated with paroxetine was included to assess the sensitivity of the study design. The therapeutic response and adverse event profile of paroxetine observed here were consistent with those reported in the literature.[30,35] Improvement in sleep quality following paroxetine treatment was also observed, although most SSRIs have been shown to cause sleep disruption (objective measures) and have no effects on subjective sleep measures.[36,37]

The positive effects of tiagabine on anxiety in patients with GAD are consistent with preliminary observations reported in the literature. Case series have shown that tiagabine, as monotherapy or augmentation therapy, reduces anxiety in patients with GAD, posttraumatic stress disorder, and panic disorder.[15–18] The positive effect of tiagabine on subjective sleep in the current trial was consistent with a double-blind, placebo-controlled study of healthy elderly subjects, in which tiagabine increased self-perceived sleep intensity and improved objective sleep quality.[19]

The observation that tiagabine improved comorbid depressive symptoms in patients with GAD is encouraging, as this is the first study to evaluate these symptoms. However, interpretation of this result must take into consideration that the present patient population had only mild depressive symptoms and were not diagnosed with a mood disorder at baseline.

This therapeutic response of tiagabine in anxiety, mood, and sleep is consistent with the drug's mechanism of action. It is well established that the $GABA_A$, $GABA_B$, and $GABA_C$ receptors are involved in anxiety, mood, and sleep.[6,38–40] By inhibiting the reuptake of GABA, tiagabine increases synaptic levels of this neurotransmitter and enhances GABA tone at GABA receptors.[13] This modulation of the GABA system suggests tiagabine may have broad clinical efficacy across many disorders.

Limitations of this trial include that this was an open-label study in which the patient population was restricted to subjects with GAD and no other psychiatric disorder. Although the patients had been newly diagnosed with GAD, they all had long-standing symptoms of anxiety. Furthermore, while a positive control with well-established efficacy in GAD was included, this study was not sufficiently powered to perform comparative statistical analyses. Lastly, the raters, but not the patients, were blinded to treatment, and, thus, patient bias in favor of paroxetine may have occurred.

In conclusion, the selective GABA reuptake inhibitor tiagabine showed significant benefit in treating the core symptoms of GAD, such as anxiety and sleep disturbances, in addition to comorbid depressive symptoms. Furthermore, tiagabine treatment was well tolerated and not associated with significant sexual dysfunction. Thus, tiagabine may be a therapeutic option for the treatment of anxiety disorders.

Drug names: paroxetine (Paxil), tiagabine (Gabatril).

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