The Selective GABA Reuptake Inhibitor Tiagabine for the Treatment of Generalized Anxiety Disorder: Results of a Placebo-Controlled Study

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Objective: To evaluate the efficacy and tolerability of tiagabine, a selective γ-aminobutyric acid (GABA) reuptake inhibitor, in adults with generalized anxiety disorder (GAD).

Method: This 8-week, randomized, double-blind, multicenter, placebo-controlled study enrolled patients with GAD (DSM-IV). Tiagabine was initiated at 4 mg/day and then flexibly dosed twice a day to a maximum dose of 16 mg/day. Study drug was tapered after week 8 in decrements of 2 mg every other day. Efficacy assessments included the Hamilton Rating Scale for Anxiety (HAM-A) and Sheehan Disability Scale. Adverse events, sexual functioning, and change in depressive symptoms were monitored. Data were collected from May 2003 to January 2004.

Results: A total of 266 patients (tiagabine, N = 134; placebo, N = 132) were included in safety analyses; 260 patients (tiagabine N = 130; placebo N = 130) were included in efficacy analyses. Tiagabine reduced symptoms of GAD according to the observed case and mixed models repeated-measures (MMRM) analyses but not the primary last-observation-carried-forward (LOCF) analysis. At final visit, the reduction from baseline in mean HAM-A total score was 11.8 for tiagabine, compared with 10.2 for placebo (LOCF analysis, p = .27). In a post hoc MMRM analysis, a significant difference in the mean reduction in HAM-A total score over the efficacy evaluation period was found, favoring tiagabine over placebo (p < .01). Tiagabine had an early onset of effect, as shown by significant reduction from baseline in mean HAM-A total score compared with placebo at week 1 (observed cases, p < .05). Tiagabine was generally well tolerated and not associated with changes in sexual functioning or depressive status. Symptoms of a discontinuation syndrome during taper were not observed.

Conclusion: The primary LOCF analysis was negative; however, results from the observed case and MMRM analyses suggest that tiagabine may be a useful treatment option for adult patients diagnosed with GAD. These findings warrant further evaluation in randomized clinical studies.

(J Clin Psychiatry 2005;66:1401–1408)

Generalized anxiety disorder (GAD) is a chronic and disabling disorder,[1] with a reported lifetime prevalence in the general population of approximately 5%.[2] GAD is characterized by excessive anxiety and worry that occur on most days, about everyday or routine activities, for a period of at least 6 months.[1] The disorder typically follows a chronic episodic pattern of remission and relapse.[3] In the Harvard-Brown Anxiety Research Program prospective study, less than 50% of patients with GAD experienced full or partial remission during 5 years of follow up, and 27% of those experienced subsequent relapse.[4] GAD has a detrimental effect on daily activities, occupational performance, interpersonal relationships, and social activities. The level of impairment reported by patients is further compounded by a high rate of psychiatric comorbidity.[5,6]

Current treatment options for GAD include the benzodiazepines, buspirone, selective serotonin reuptake inhibitors (SSRIs), and the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine.[7] Though effective, benzodiazepines can be associated with the development of physiologic dependence after a few weeks of therapy as well as abuse liability in predisposed individuals.[8,9] Buspirone, although demonstrating efficacy in clinical trials, has been met with mixed success in clinical practice.[10]

SSRIs and SNRIs are also effective medications for many patients with GAD; however, a significant proportion of patients either do not respond fully to these agents or experience adverse events, including weight gain and sexual dysfunction, that can lead to discontinuation of treatment and a return of GAD symptoms.[11] Additional treatment options that are well tolerated and appropriate for long-term treatment are warranted.

γ-Aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the central nervous system and has been implicated in the pathophysiology of GAD.[12,13] GABA counterbalances the excitatory effects of glutamate, and the homeostatic mechanisms between these systems act to prevent excessive neuronal hyperexcitability. Binding of benzodiazepines to the GABA$_A$ receptor increases the affinity of the GABA binding site for GABA, thereby enhancing the effect of endogenous GABA. Neuroimaging studies have shown reduced levels of GABA and reduced GABA$_A$–benzodiazepine-receptor binding in patients with anxiety disorders, indicating dysfunction of the GABA system in these disorders.[12,13] Given these findings and the utility of benzodiazepines, agents that facilitate GABA neurotransmission by an alternative mechanism of action may be useful in the treatment of anxiety disorders.

Tiagabine is a selective GABA reuptake inhibitor that increases synaptic availability of GABA via selective inhibition of the GAT-1 GABA transporter, thus prolonging the effect of endogenous GABA in the synapse.[14,15] Results of an open-label study suggest that tiagabine reduces symptoms of anxiety in patients with GAD.[16] This double-blind, placebo-controlled study evaluated the efficacy and tolerability of tiagabine in adult patients with GAD.

METHOD

Study Design

This 8-week, double-blind, multicenter, placebo-controlled study randomly assigned patients to a flexible-dose regimen of tiagabine or matching placebo. Tiagabine was administered in divided doses: 1 dose with breakfast and 1 dose in the evening (approximately 9:00 p.m.) with a snack. Tiagabine was initiated at 4 mg/day for the first week and then individually titrated through week 6, in weekly increments of up to 4 mg, to a maximum dose of 16 mg/day. Dosages were titrated upward unless, in the investigator's judgment, a dose increase was (1) inadvisable due to recurrent or persistent adverse events, (2) not expected to increase efficacy, or (3) not desired by the patient. The dose established at week 6 could not be increased during weeks 7 and 8. Throughout the efficacy evaluation period, dose reductions (in 2-mg decrements per week) were permitted if patients were unable to tolerate the drug because of adverse events. At the end of the efficacy evaluation period, study drug was tapered in decrements of 2 mg every other day (over a 2- to 14-day period), alternating between the morning and evening dose.

Patient Selection

Patients aged 18 to 64 years who met DSM-IV criteria for GAD, as determined by a psychiatric evaluation that included the Mini-International Neuropsychiatric Interview,[17] were enrolled in the study. To be included in the study, patients had to meet the following criteria at screening and baseline visits: a score of ≥ 18 on the 14-item Hamilton Rating Scale for Anxiety (HAM-A),[18] with a score of ≥ 2 on item 1 (anxious mood) and on item 2 (tension); a score of ≥ 8 on the Hospital Anxiety and Depression Scale (HADS) anxiety subscale; a Covi Anxiety Scale[19] score that was greater than the Raskin Depression Scale[20] score; and a score of ≥ 4 (indicative of at least moderate illness) on the Clinical Global Impressions-Severity of Illness scale (CGI-S).[21]

Patients were excluded from the study for the following reasons: a Montgomery-Asberg Depression Rating Scale (MADRS)[22] total score > 20 at screening or baseline; a diagnosis of any primary psychiatric disorder other than GAD within the previous 6 months; a previous primary diagnosis of obsessive-compulsive disorder, bipolar disorder, mental retardation, antisocial personality disorder, or psychotic disorder; a clinical assessment of current risk of suicide (MADRS item 10 score > 3); or alcohol or substance abuse within 3 months or dependence within 6 months of study entry. Patients who had previously not responded to 2 or more adequate (in dose and duration) courses of treatment (pharmacotherapy or cognitive-behavioral therapy) for GAD and patients who had a decrease of ≥ 50% in HAM-A total score or HADS anxiety subscale score between screening and baseline visit were also excluded. Patients were also ineligible for inclusion if they had previously received tiagabine, had received any other investigational drug within 4 weeks of the screening visit, were participating in a concurrent clinical trial, or had undergone electroconvulsive therapy within 3 months of the screening visit.

Patients were required to be free of drugs with known or putative psychotropic properties, including herbal medications, for 2 weeks (6 weeks for fluoxetine and 12 weeks for depot antipsychotic therapy) prior to the screening and throughout the study. Psychotherapeutic intervention could not have been initiated within 2 months of screening.

Efficacy Assessments

Efficacy was assessed using change from baseline on the HAM-A total score, HAM-A anxiety and tension item scores, and HADS anxiety subscale score at weeks 1–4, 6, and 8. Patients' overall clinical condition was evaluated using the CGI-S at baseline and the CGI-Improvement

scale (CGI-I)[21] at weeks 1–4, 6, and 8. Impact on patient functioning within the domains of work, social, and family life was evaluated using the Sheehan Disability Scale (SDS)[23] at baseline and at weeks 4 and 8.

Safety and Tolerability Assessments

The overall safety and tolerability of tiagabine was assessed throughout the study by recording adverse events and vital signs. Changes in depressive symptoms were monitored using the MADRS, which was administered at baseline and at weeks 1–4, 6, and 8. Sexual functioning was evaluated by the Massachusetts General Hospital Sexual Functioning Questionnaire (MGSQ),[24] completed at baseline and at week 8. Weight was recorded at baseline and at week 8. The Physician Withdrawal Checklist (PWC)[25] was administered at week 8, by telephone contact after each dose reduction during taper, and at the final follow-up visit to monitor for symptoms associated with a discontinuation syndrome.

Statistical Analysis

Randomly assigned patients who received at least 1 dose of study drug were included in the safety analysis. Randomly assigned patients who received at least 1 dose of study drug and had at least 1 postbaseline efficacy assessment were included in the efficacy analysis. The dose taken most frequently by a patient during the efficacy evaluation period prior to taper was used to describe the distribution of doses.

The primary efficacy measure was the change from baseline in HAM-A total score to final visit (last observation in the efficacy evaluation period carried forward [LOCF]). The comparison between tiagabine and placebo was made using an analysis of covariance (ANCOVA) with baseline score, treatment, and center in the model. In addition, a post hoc analysis to compare the mean treatment effect across the entire study period was performed on changes from baseline in HAM-A total score using a mixed models repeated measures (MMRM) analysis. This method uses all available data and thus is consistent with an intent-to-treat approach.[26] Change from baseline in mean HAM-A total score for the tiagabine and placebo groups was also compared at each clinical visit (weeks 1, 2, 3, 4, 6, and 8) using observed data (cases) at the particular visit. Comparisons of the proportion of responders, according to the HAM-A total score ($\geq$ 50% reduction from baseline) and the CGI-I rating ("very much improved" or "much improved"), and the proportion of patients who achieved remission (HAM-A total score $\leq$ 7) all at final visit were made using a Cochran-Mantel-Haenszel χ^2 test adjusted for center. Comparisons of the change from baseline in HAM-A anxiety and tension items scores, HAM-A psychic and somatic anxiety subscales scores, HADS anxiety subscale score, and SDS domain and total scores between tiagabine and placebo were

also performed using ANCOVA with baseline score, treatment, and center in the model. All tests were 2-tailed at a significance level of .05. Data were collected from May 2003 to January 2004.

The study was approved by individual institutional review boards at each site and conducted in accordance with the current revision of the Declaration of Helsinki and Good Clinical Practice Guidelines. All patients provided written informed consent to participate.

RESULTS

Patient Disposition

A total of 272 patients were randomly assigned to treatment (tiagabine, N = 138; placebo, N = 134). Of these, 266 patients received at least 1 dose of study medication (tiagabine, N = 134; placebo, N = 132) and were included in the safety analyses, while 260 (tiagabine, N = 130; placebo, N = 130) had at least 1 postbaseline efficacy assessment and were included in the efficacy analyses. Patient disposition and reasons for discontinuation are shown in Figure 1.

Baseline Patient Characteristics

Patients randomly assigned to tiagabine or placebo were well matched with regard to demographics and severity of illness (Table 1). At baseline, 49% of patients (65/134) in the tiagabine group were rated as "markedly or severely ill" on the CGI-S, compared with 48% of patients (63/132) in the placebo group. Severity of symptoms of anxiety (HAM-A total and HADS anxiety subscale scores), depressive symptoms (MADRS total score), and patients' degree of disability (SDS) were also similar between the tiagabine- and placebo-treated groups at baseline.

Dosing

The mean dose of tiagabine during the efficacy evaluation period was 10.2 mg/day (range, 2–16 mg/day). The distribution of tiagabine doses taken most frequently during the study prior to taper was as follows: 2 to 4 mg, 19% (25/134); 6 to 8 mg, 31% (41/134); 10 to 12 mg, 22% (29/134); 14 to 16 mg, 29% (39/134).

Efficacy

At final visit (LOCF), the reduction from baseline in mean HAM-A total score was 11.8 for tiagabine compared with 10.2 for placebo, which did not reach statistical significance (p = .27; Table 2). In a post hoc MMRM analysis, however, a statistically significant difference in the mean reduction in HAM-A total score over the efficacy evaluation period was found, favoring tiagabine over placebo (p < .01). Moreover, by observed case analysis, a significant reduction in HAM-A total score was noted for study completers at week 8 (p < .05; Figure 2). An addi-

Figure 1. Patient Disposition in a Trial of Tiagabine for Generalized Anxiety Disorder
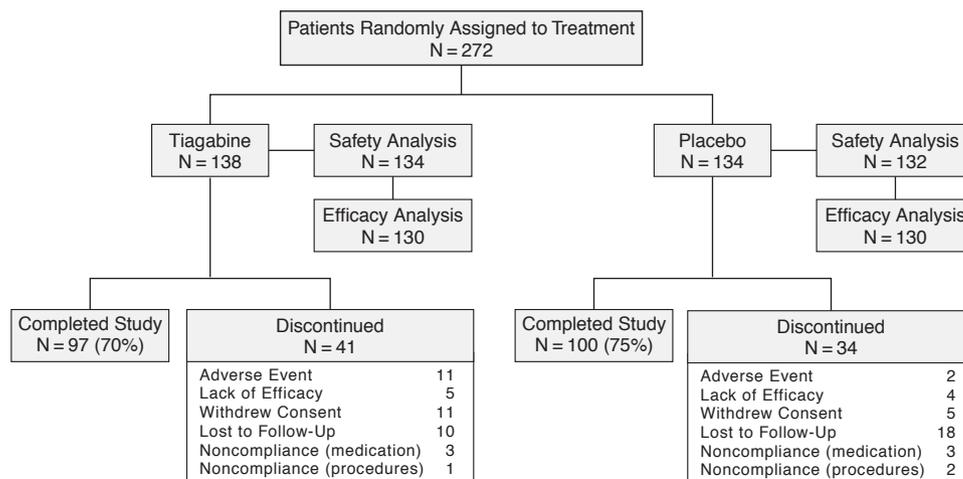

Table 1. Patient Demographic and Clinical Characteristics at Baseline in a Study of Tiagabine for Generalized Anxiety Disorder (GAD)

Characteristic	Tiagabine (N = 134)	Placebo (N = 132)
Age, mean (range), y	37.3 (19.0–65.0)	37.2 (19.0–67.0)
Sex, N (%)		
Male	58 (43)	57 (43)
Female	76 (57)	75 (57)
Weight, mean (range), kg	78.5 (44.9–145.1)	80.5 (44.9–167.8)
Duration of GAD, mean (range), y[a]	14.0 (0.8–60.0)	12.8 (0.7–50.0)
At least 1 comorbid psychiatric disorder, N (%)[b]	15 (11)	11 (8)
CGI-S rating, N (%)		
Moderately ill	69 (51)	69 (52)
Markedly ill	60 (45)	59 (45)
Severely ill	5 (4)	4 (3)
Score, mean (SD)		
HAM-A total[c]	26.1 (4.6)	25.7 (4.8)
HADS anxiety subscale[c]	13.8 (3.0)	13.7 (2.9)
MADRS total	14.9 (3.5)	14.8 (3.5)
SDS total[c]	17.8 (6.0)	17.7 (5.9)

[a]N = 131 in the placebo group.
[b]Psychiatric comorbidities (≥ 3% of patients): major depressive disorder (tiagabine, 2%; placebo, 5%); dysthymia (tiagabine, 3%; placebo, 0%); social anxiety disorder (tiagabine, 3%; placebo, 4%).
[c]N = 130 in both the tiagabine and placebo groups.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HADS = Hospital Anxiety and Depression Scale, HAM-A = Hamilton Rating Scale for Anxiety, MADRS = Montgomery-Asberg Depression Rating Scale, SDS = Sheehan Disability Scale.

Table 2. Efficacy Measures at Week 8 (observed cases) and Final Visit (LOCF) in a Study of Tiagabine for Generalized Anxiety Disorder[a]

Measure		Tiagabine	Placebo	p Value
HAM-A total score	Week 8	−13.2	−10.7	.046
	Final visit	−11.8	−10.2	.27
Anxious mood	Week 8	−1.5	−1.1	.021
	Final visit	−1.3	−1.1	.16
Tension	Week 8	−1.3	−1.1	.13
	Final visit	−1.1	−1.0	.51
Psychic anxiety	Week 8	−7.6	−5.6	.011
	Final visit	−6.5	−5.3	.11
Somatic anxiety	Week 8	−5.6	−5.1	.38
	Final visit	−5.2	−5.0	.84
HADS anxiety subscale score	Week 8	−5.1	−4.0	.039
	Final visit	−4.7	−4.0	.22
SDS total score	Week 8	−6.7	−4.7	.011
	Final visit	−6.0	−4.8	.17
HAM-A responders, % (N/N)[b]	Week 8	55 (52/95)	38 (39/103)	.019
	Final visit	45 (58/130)	36 (47/130)	.22
HAM-A remission, % (N/N)[c]	Week 8	33 (31/95)	23 (24/103)	.15
	Final visit	26 (34/130)	25 (32/130)	.92
CGI-I responders, % (N/N)[d]	Week 8	57 (54/95)	44 (45/130)	.081
	Final visit	50 (65/130)	42 (54/103)	.22

[a]All scores are shown as change from baseline.
[b]HAM-A response: ≥ 50% reduction in total score from baseline.
[c]HAM-A remission: total score ≤ 7.
[d]CGI-I response: score of 1 or 2 ("very much" or "much" improved).
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, HADS = Hospital Anxiety and Depression Scale, HAM-A = Hamilton Rating Scale for Anxiety, LOCF = last observation carried forward, SDS = Sheehan Disability Scale.

tional finding from the observed case analysis was an early onset of effect for tiagabine, as shown by significant reductions from baseline in mean HAM-A total score compared with placebo at week 1 (p < .05; Figure 2).

Results for the following secondary efficacy measures generally showed favorable effects for tiagabine over placebo by observed case analyses but not by LOCF analyses (Table 2). At week 8, 55% of patients (52/95) in the tiaga-

bine group compared with 38% of patients (39/103) in the placebo group were responders (≥ 50% reduction from baseline in HAM-A score; p = .02), and 33% of patients (31/95) receiving tiagabine achieved remission (HAM-A total score ≤ 7) compared with 23% of patients (24/103) receiving placebo (p = .15; Table 2) by observed case analyses. Similarly, 57% of patients (54/95) in the tiagabine group compared with 44% of patients (45/103) in

Figure 2. Effect of Tiagabine on HAM-A Total Score in Patients With Generalized Anxiety Disorder[a]
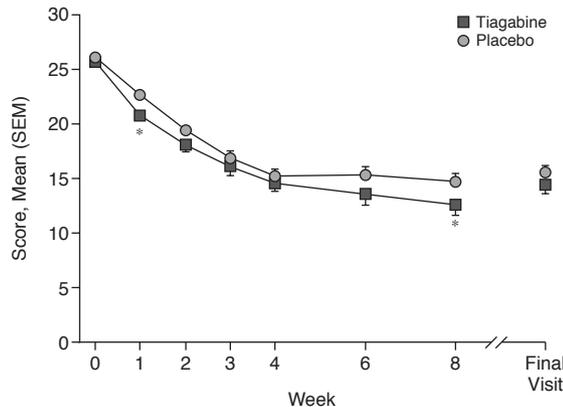
[a]Weekly data as observed cases; final visit as last postbaseline assessment.
*p < .05 vs. placebo.
Abbreviation: HAM-A = Hamilton Rating Scale for Anxiety.

Figure 3. Effect of Tiagabine on HAM-A Total, Subscale, and Item Scores at Week 8 in Patients With Generalized Anxiety Disorder[a]

[a]Week 8 data as observed cases.
*p < .05 vs. placebo.
Abbreviation: HAM-A = Hamilton Rating Scale for Anxiety.

Figure 4. Effect of Tiagabine on Sheehan Disability Scale (SDS) Total and Domain Scores at Week 8 in Patients With Generalized Anxiety Disorder[a]

[a]Week 8 data as observed cases.
*p < .05 vs. placebo.

the placebo group were responders (i.e., "very much improved" or "much improved" on the CGI-I; p = .08).

Patients in the tiagabine group had significantly greater mean reductions from baseline at week 8 compared with placebo on the HAM-A anxious mood item score (tiagabine, 1.5; placebo, 1.1; p < .05) and the psychic anxiety subscale score (tiagabine, 7.6; placebo, 5.6; p < .05; Table 2 and Figure 3), though not on the mean somatic anxiety subscale score and tension item score.

Significant reductions in symptoms of GAD were also observed on the HADS anxiety subscale (Table 2). The tiagabine group had significantly greater mean reductions from baseline on the HADS anxiety subscale score compared with placebo at week 6 (tiagabine, 5.1; placebo, 3.8; p < .05) and at week 8 (tiagabine, 5.1; placebo, 4.0; p < .05).

Tiagabine also improved patients' overall functioning according to SDS domain and total scores (Table 2 and Figure 4). At week 8, the mean reduction from baseline in the SDS total score was significantly greater in the tiagabine group (6.7) compared with placebo (4.7; p < .05). Patients receiving tiagabine reported greater reductions from baseline in all domains at week 8 compared with placebo, with a statistically significant difference observed for the work domain (tiagabine, 2.3; placebo, 1.4; p < .05).

Tolerability

Tiagabine was generally well tolerated. The most commonly reported adverse events during the study period were dizziness (34%), headache (30%), and nausea (22%) for patients receiving tiagabine, and headache (27%) and nausea (20%) for patients receiving placebo (Table 3). Those adverse events experienced by at least 5% of pa-

tients receiving tiagabine and with at least twice the frequency as in patients receiving placebo were dizziness (34% vs. 8%), somnolence (15% vs. 5%), disturbance in attention (6% vs. 2%), dyspepsia (6% vs. 2%), anxiety (5% vs. 1%), and asthenia (5% vs. 2%). Most patients (78%) reported adverse events, which were generally mild or moderate in severity. Eleven patients (8%) receiving tiagabine withdrew from the study because of adverse events, the most common reasons being dizziness (N = 4) and fatigue (N = 2).
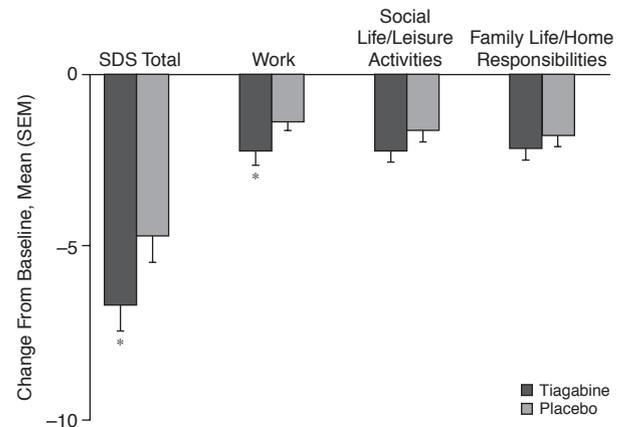
Tiagabine did not seem to adversely affect patients' sexual functioning, as there was no significant difference

Table 3. Patients With Generalized Anxiety Disorder Reporting Adverse Events (frequency ≥ 5%) During Tiagabine Versus Placebo Administration

Adverse Event	Tiagabine, N (%) (N = 134)	Placebo, N (%) (N = 132)
Dizziness	45 (34)	11 (8)
Headache	40 (30)	36 (27)
Nausea	30 (22)	26 (20)
Fatigue	23 (17)	12 (9)
Nasopharyngitis	21 (16)	19 (14)
Somnolence	20 (15)	7 (5)
Diarrhea	18 (13)	10 (8)
Insomnia	11 (8)	9 (7)
Dry mouth	9 (7)	6 (5)
Disturbance in attention	8 (6)	2 (2)
Dyspepsia	8 (6)	3 (2)
Irritability	8 (6)	8 (6)
Anxiety	7 (5)	1 (1)
Asthenia	7 (5)	2 (2)
Sedation	7 (5)	5 (4)
Constipation	5 (4)	6 (5)
Vomiting	4 (3)	6 (5)
Paraesthesia	3 (2)	6 (5)
Influenza	5 (4)	7 (5)

Table 4. Effect of Tiagabine on Safety Variables in Patients With Generalized Anxiety Disorder

Variable	Tiagabine (N = 134) Baseline Mean (SD)	Tiagabine Final Visit Mean (SD)	Placebo (N = 132) Baseline Mean (SD)	Placebo Final Visit Mean (SD)
Weight, kg	78.6 (20.5)	78.6 (20.1)	80.5 (22.2)	81.1 (22.9)
MGSQ score[a]				
Men[b]	15.3 (6.2)	14.8 (6.5)	14.7 (5.8)	14.2 (6.0)
Women[c]	15.3 (5.9)	12.4 (5.6)	15.2 (5.0)	13.4 (5.5)
MADRS score[d]	14.9 (3.5)	10.9 (7.7)	14.8 (3.5)	11.9 (7.4)

[a]A decrease indicates improvement.
[b]Number of male patients with MGSQ scores at baseline and final visit: placebo, 55 and 46, respectively; tiagabine, 57 and 46, respectively.
[c]Number of female patients assessed at baseline and final visit: placebo, 70 and 58, respectively; tiagabine, 65 and 53, respectively.
[d]Number of patients assessed at final visit: placebo, 132; tiagabine, 133.
Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, MGSQ = Massachusetts General Hospital Sexual Functioning Questionnaire.

Figure 5. Effect of Tiagabine on Physician Withdrawal Checklist Total Score at Week 8 (or early termination), Change From Week 8 to Follow-Up, and Maximum Change From Week 8 in Patients With Generalized Anxiety Disorder[a]
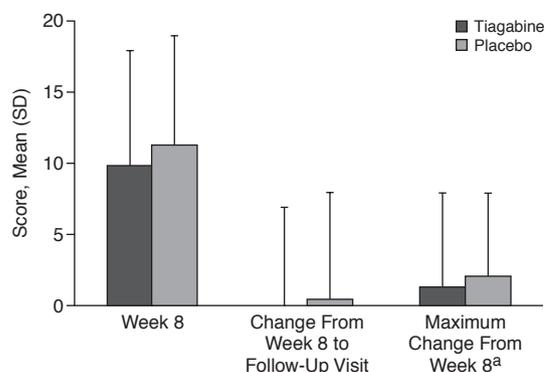
[a]Maximum value across all telephone contacts during the taper and follow-up visit.

in the mean change from baseline in MGSQ scores at final visit compared with placebo (Table 4). Tiagabine was not associated with any worsening of depressive status (Table 4), but rather, there was a trend toward improvement in mood, as shown by the mean reduction from baseline in MADRS total score at final visit (tiagabine, 4.0; placebo, 2.8). Patients receiving tiagabine did not experience weight gain. There was no significant difference in the mean change from baseline in weight at final visit compared with placebo (tiagabine, 0.2; placebo, 0.4; Table 4). No mean changes from baseline in vital signs were observed over the course of the study in the tiagabine group.

The most commonly reported adverse events during the drug-tapering period were nausea (7%) and nasopharyngitis (7%) for patients receiving tiagabine and headache (10%) and nasopharyngitis (7%) for patients receiving placebo.

Patients receiving tiagabine did not experience symptoms associated with a discontinuation syndrome during taper. There was no significant difference in mean change from week 8 in PWC score to the follow-up visit compared with placebo (tiagabine, 0.0; placebo, 0.5; Figure 5). Similarly, no significant differences in mean maximum change from week 8 across all telephone contacts during the taper and the follow-up visit were observed between tiagabine and placebo (tiagabine, 1.4; placebo, 2.1).

DISCUSSION

In this randomized, double-blind, placebo-controlled study, the efficacy and tolerability of tiagabine were evaluated in adults with GAD. The primary LOCF analysis was negative; however, results from the observed case and MMRM analyses suggest that tiagabine may be a useful treatment option for adult patients diagnosed with GAD. Tiagabine reduced symptoms of GAD over 8 weeks of treatment, with an early onset of effect. It was generally well tolerated, with most adverse events being mild to moderate in severity. Patients receiving tiagabine did not experience changes in sexual functioning or weight gain, which have been associated with the SSRIs and SNRIs,[11] or treatment-emergent depression or withdrawal symptoms during discontinuation, which are associated with benzodiazepines.

The efficacy of tiagabine in this study is within the range reported for currently approved treatment options. In 2 large, placebo-controlled studies, mean reductions in HAM-A total scores of approximately 12 points with the

SSRI paroxetine and 10 points with placebo at week 8 have been reported, with the onset of effect occurring at week 6 or beyond.[27,28] In these same studies, up to 68% of patients were responders according to CGI ratings (compared with 47% in the placebo group) and up to 43% of patients achieved remission (compared with 23% in the placebo group).

In a pooled analysis of 5 placebo-controlled clinical studies, mean reductions in HAM-A total scores of 12.7 were reported for the SNRI venlafaxine and 9.8 for placebo,[29] with an onset of effect observed at week 1.[30] Additional analyses with the same pooled data found that 56% of patients receiving venlafaxine were responders according to HAM-A criteria (compared with 39% of placebo) and 31% achieved remission (compared with 18% of placebo).[31]

Benzodiazepines also have been found to reduce mean HAM-A total scores by a similar magnitude (approximately 13 points), with responder rates of 70%, in addition to having a rapid onset of effect at week 1[32,33] as was noted for tiagabine in the current study.

A contributing factor to the observed discrepancy between the results of the final visit analyses (LOCF) and the completer analysis (observed cases) at week 8 is that premature discontinuations in the tiagabine treatment group tended to occur earlier than those in the placebo group. For example, 24 (59%) of the 41 premature discontinuations occurred by week 4 in the tiagabine group, compared with 11 (32%) of the 34 in the placebo group. This fact, coupled with the observed and important treatment effect, is likely to have introduced bias into the LOCF imputation procedure used for the final visit analyses.

The differential withdrawal rate over time observed in the present study may be due to a limitation of the study design. Because the study was designed with an intent to explore doses associated with a patient's maximum clinical response, the titration criteria encouraged physicians to increase the dose until the patient achieved a CGI-I rating of 1 ("very much improved"), or until tolerability precluded further dose increases. As a result, the dose of tiagabine was often increased weekly in 4-mg increments. This rapid dose escalation quite likely resulted in a greater number of early discontinuations in the tiagabine group, giving rise to the differential withdrawal rate. Future studies of tiagabine in GAD will utilize a more conservative upward titration schedule than the current trial in order to reduce dropouts associated with early rapid dose escalation.

In conclusion, in this randomized, double-blind, placebo-controlled study, tiagabine reduced the symptoms of GAD, with an early onset of effect according to the observed case and MMRM analyses, although not the LOCF analysis. Tiagabine was generally well tolerated and was not associated with changes in sexual function-ing, weight, or depressive status. Symptoms of a discontinuation syndrome during taper were not observed. Although the primary LOCF efficacy analysis was negative, results from the MMRM and observed case analyses indicate that tiagabine shows promise as a novel treatment option for adult patients with GAD. Additional clinical studies are underway to confirm and further characterize the efficacy and tolerability of tiagabine for the treatment of patients with GAD.

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