Annals of Clinical Psychiatry, 19[1]:25–30, 2007

ISSN: 1040-1237 print / 1547-3325 online
DOI: 10.1080/10401230601163535

informa
healthcare

An Open-Label Study to Evaluate Switching from an SSRI or SNRI to Tiagabine to Alleviate Antidepressant-Induced Sexual Dysfunction in Generalized Anxiety Disorder

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Background. *This study investigated tiagabine monotherapy in subjects with generalized anxiety disorder (GAD) who had been switched from selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) as a result of antidepressant-induced sexual dysfunction.*

Methods. *Adults with DSM-IV GAD, an adequate therapeutic response (≥50% decrease in Hamilton Rating Scale for Anxiety [HAM-A] total score) to SSRI or SNRI and sexual dysfunction were switched to open-label tiagabine 4–12 mg/day for 14 weeks. Assessments included the HAM-A, Hospital Anxiety & Depression Scale (HADS) and the Arizona Sexual Experiences Scale (ASEX); assessments were made at baseline and at Weeks 4, 8, and 14.*

Results. *Twenty six subjects were included in the analysis. Tiagabine showed no worsening in baseline symptoms of GAD, with non-significant changes from baseline in mean HAM-A total scores and HADS Anxiety and Depression subscale scores. There was a significant ($p < 0.001$) reduction in ASEX total scores from baseline following tiagabine, indicating an alleviation of sexual dysfunction. Tiagabine was reasonably tolerated; the most commonly reported adverse events were dizziness/light headedness (n = 6; 23%), nausea (n = 6; 23%) and fatigue (n = 2; 8%).*

Conclusions. *Tiagabine may be useful in subjects who respond to previous antidepressant therapy but develop sexual dysfunction as an adverse event.*

INTRODUCTION

Generalized anxiety disorder (GAD) is among the most common psychiatric disorders in the United States, with an estimated lifetime prevalence of approximately 5% (1,2). Characterized by a state of excessive, pervasive and uncontrolled worry, GAD follows a chronic course where symptoms may persist for up to 20 years or more (3,4). GAD is associated with a significant impairment of patient functioning and quality of life (5), as well as an increased risk of comorbidity with other psychiatric disorders such as major depression (6). The impact of GAD on morbidity and mortality makes the disorder an important public health concern (7).

Supported by Cephalon, Inc., Frazer, PA.

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The selective serotonin reuptake inhibitors (SSRIs; e.g., paroxetine, escitalopram) and serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine have well-documented efficacy and are considered first-line treatment for patients with GAD (8). However, even in those patients who receive SSRI/SNRI treatment of adequate dose and duration, up to 45% do not achieve response (8), and up to 65% do not achieve remission (9). In addition, even when patients show a good response to therapy, compliance with treatment is often poor (10), while clinical studies have reported discontinuation rates of almost 15% as a result of adverse events (11).

Impairment of sexual functioning is frequently associated with psychiatric disorders such as major depression and anxiety. For example, as many as 70% of patients with depression experience problems with sexual functioning (12). It is important to recognize that sexual activity is important to patients and that their psychiatric disorder should be managed in a way that optimizes sexual function (13). However, the onset or worsening of sexual dysfunction is also increasingly recognized as an adverse event associated with antidepressant therapy, and one that is an important contributor to treatment non-compliance and impairment of quality of life (14,15). In particular, antidepressants with predominantly serotonergic effects, such as the SSRIs and SNRIs have generally been associated with the highest rates of treatment-emergent sexual dysfunction (16). At present, however, there are no guidelines to inform clinicians on the management of such patients.

In addition to serotonin and norepinephrine, the neurotransmitter γ-aminobutyric acid (GABA), the primary inhibitory neurotransmitter in the central nervous system, has been implicated in the pathophysiology of GAD (17,18). Benzodiazepines enhance the inhibitory effects of GABA by binding to post-synaptic $GABA_A$ receptors and increasing their affinity for GABA. The anxiolytic effects of benzodiazepines suggest that other agents that also facilitate GABA neurotransmission may be useful in the treatment of anxiety.

Tiagabine is a selective GABA reuptake inhibitor (SGRI) that increases synaptic GABA availability by selective inhibition of the GAT-1 GABA transporter (19,20). Results from previous studies (an open-label study using paroxetine as a positive control and a double-blind, placebo-controlled study) suggest that tiagabine reduces symptoms of anxiety in patients with GAD (21,22). Furthermore, in both of these studies, tiagabine was not associated with changes in sexual functioning, which is in keeping with its lack of effect on the serotonergic system.

The aim of this study was to evaluate the effect of tiagabine monotherapy in patients with GAD who had been switched from an SSRI or SNRI as a result of antidepressant-induced sexual dysfunction. The authors hypothesized that the removal of the initial SSRI/SNRI and conversion to tiagabine monotherapy would (1) allow for the alleviation of serotonergic induced sexual dysfunction (2) maintain and not lessen current SSRI/SNRI response levels (3) not induce a depressive state.

METHODS

Study Design and Patient Selection

This was a 14-week, open-label study conducted at a single center in the United States. All subjects provided written informed consent, and approval was obtained from the institutional review board. Male and female adults aged 18–64 years with a DSM-IV diagnosis of GAD as determined by the Mini International Neuropsychiatric Inventory (23) were eligible to be enrolled in the study. Subjects were required to have been taking a single SSRI or SNRI for ≥4 weeks and achieved an adequate therapeutic response (defined as an improvement of ≥50% based on self report). Subjects were also required to report a chronological emergence of sexual dysfunction (decreased sex drive, arousal, lubrication, or onset of impotence, anorgasmia or delayed ejaculation) following SSRI/SNRI initiation, and have a Hamilton Rating Scale for Anxiety (HAM-A) (24) total score of <18 (mild symptoms only after SSRI/SNRI monotherapy). Subjects were excluded from the study if they met any of the following criteria: presence of any serious, unresolved or unstable medical and/or psychiatric condition, or a medical condition causing sexual dysfunction; a history of >1 depressive episode or had not been in remission for >1 year; taking sildenafil or any other sexually enhancing agent; previous participation in a clinical study with tiagabine or previous treatment with tiagabine; suicidal behavior in the previous year or current lethality symptoms at time of screening; use of an investigational drug within 1 month of the screening visit or participation in a clinical study; presence of a disorder likely to interfere with study drug absorption; pregnancy or lactation; alcohol or sedative dependence within the previous year or any other substance abuse/dependence in the previous 3 months, including heavy caffeine (>8 cups per day) or nicotine use (>2 packs per day) which may contribute to the anxious state.

Dosing

Tiagabine was titrated based on individual response and tolerability, while the subjects' SSRI/SNRI regimen was tapered downward until Week 4 when all patients were no longer receiving the SSRI/SNRI and the full dose of tiagabine was in place. Tiagabine was administered in uneven divided doses starting at 4 mg/day (2 mg qAm with breakfast and 2 mg qHS with a snack for 5 days). From Day 6, tiagabine could be increased to 8 mg/day (2 mg qAm and 6 mg qHS) at the discretion of the investigator and patient. If required, the dose could be increased from Day 13 onward to 12 mg/day (4 mg qAm and 8 mg qHS). At the discretion of the investigator, the dose could be lowered to alleviate adverse events. Upon completion of the study, patients could opt to remain on tiagabine or be titrated back onto their previous medication (SSRI/SNRI).

Study Assessments

The severity of anxiety and depressive symptoms was evaluated using the HAM-A and the Hospital Anxiety & Depression Scale (HADS) (25), respectively. Sexual functioning was assessed using the Arizona Sexual Experiences Scale (ASEX) (26). The ASEX is a patient-rated scale comprising five questions with responses measured on a six-point scale. The total score varies from a minimum of 5 (indicating normal sexual functioning) to a maximum of 30 (indicating complete sexual dysfunction). The questions are the same for male and female patients, except for question 3. Assessments were made at baseline of tiagabine administration and at Weeks 4, 8, and 14 during open-label therapy. The tolerability of tiagabine was assessed throughout the study by recording patient-reported adverse events.

Statistical Analyses

Patients with at least one post-baseline tolerability and efficacy assessment were included in the efficacy dataset and analyzed by visit using observed data, and at final visit using the last post-baseline observation (LOCF) available for each patient (final visit). Assessments were made at baseline of tiagabine administration and at weeks 4, 8, and 14. Comparisons with baseline in HAM-A, HADS and ASEX were performed using repeated measures ANOVA with Bonferroni adjustment for the repeated measures. Patients who received at least one dose of tiagabine were included in the safety analyses.

RESULTS

Subjects

A total of 26 GAD subjects with an average of 95.71 weeks (Range: 3 months–6 years) of SSRI/SNRI treatment had at least one evaluation after initiating tiagabine and are included in this LOCF analysis. Demographic and baseline characteristics of the patients are summarized in Table 1. At the final visit, the mean (±SD) dose of tiagabine was 8.28 ± 5.4 mg/day (range 4–12 mg/day).

Outcomes

The effects of tiagabine on symptoms of anxiety as assessed by the HAM-A are shown in Figure 1. The level of improvement in symptoms of GAD among subjects entering the study was maintained during the 14 weeks of treatment with tiagabine. The mean HAM-A baseline score was 9.1 ± 1.2; the mean total score was lower Week 4 and 14 (mean change from baseline 2.0 and 2.2, respectively), and significantly lower at Week 8 (mean change from baseline 3.7; $p < 0.002$). There were also non-significant reductions from baseline in the mean HADS-Anxiety subscale scores at each time point (Figure 2).

A statistically and clinically significant improvement in sexual functioning was reported throughout the study following treatment with tiagabine ($p < 0.001$ at each study visit) (Figure 3). The mean total ASEX score at baseline was 21.6 ± 0.9 and was reduced to 16.7 ± 1.4 at Week 4, 15.8 ± 1.4 at Week 8 and 15.7 ± 1.3 at final visit. Although subjects were not diagnosed with a mood disorder, tiagabine reduced depressive symptoms, as

Table 1 Patient Demographics and Baseline Clinical Characteristics ($n = 26$)

Characteristic	N = 26
Gender, n (%)	
Male	11 (42)
Female	15 (58)
Age, mean ± SD years	45 ± 12.9
Baseline HAM-A score (mean ± SEM)	9.1 ± 1.2
Baseline HADS-Anxiety subscale score (mean ± SEM)	8.4 ± 0.8
Baseline HADS-Depression subscale score (mean ± SEM)	4.4 ± 0.7
Baseline ASEX score (mean ± SEM)	21.6 ± 0.9

HAM-A, Hamilton Anxiety Rating Scale for Anxiety; HADS, Hospital Anxiety & Depression Scale; ASEX, Arizona Sexual Experience Scale.

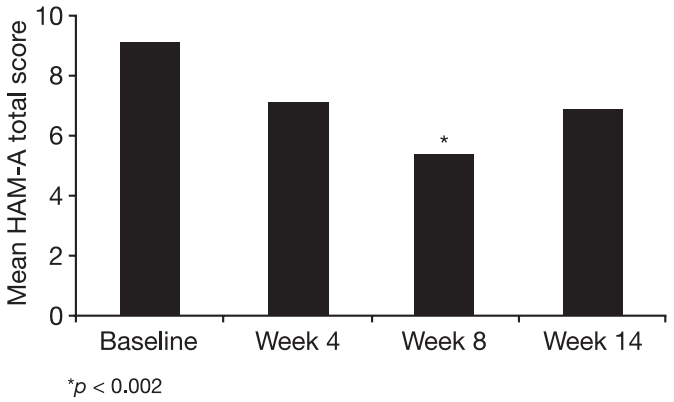

Figure 1 Mean HAM-A Total Scores in Patients Receiving Tiagabine ($n = 26$).

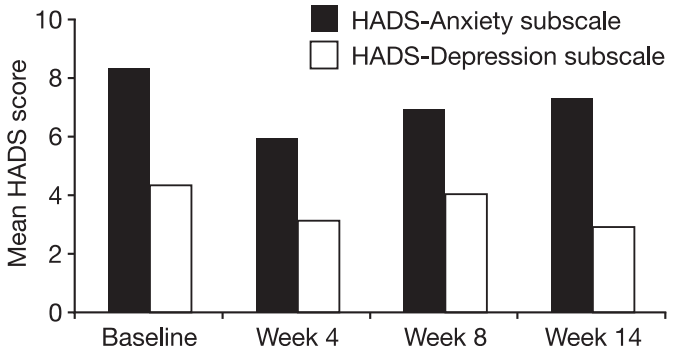

Figure 2 Mean Scores on the Patient-rated HADS-Anxiety Subscale and HADS-Depression Subscale ($n = 26$).

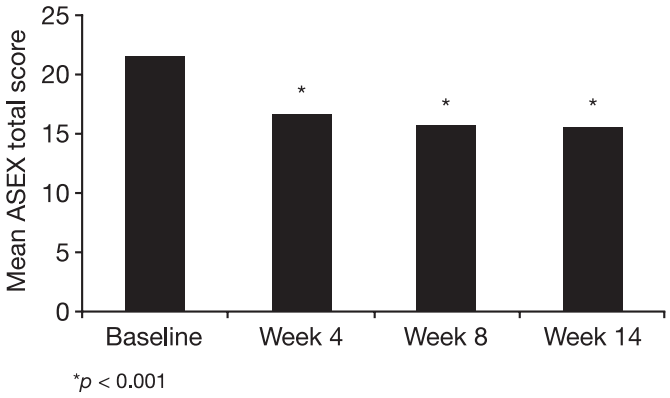

Figure 3 Mean Total Scores on the Patient-rated ASEX Scale (n = 26).

assessed by the HADS-Depression subscale, although the changes were not significantly different from baseline (Figure 2). The HADS-Depression scores were low to begin with.

Tolerability

A total of 17 subjects completed the full 14 weeks of open-label therapy. Of those who did not complete the study, eight subjects withdrew because of adverse events (listed below), and one subject left as a result of injuries sustained in a motorcycle accident. Tiagabine was generally well tolerated. The most commonly reported adverse events were dizziness/lightheadedness (n = 6; 23%), nausea (n = 6; 23%), and fatigue (n = 2; 8%), and these were mild to moderate in severity. Tiagabine did not induce depression as an adverse event.

DISCUSSION

The results of this study suggest that in subjects with GAD who had been receiving an SSRI or SNRI with reasonable clinical effectiveness, but who had developed sexual dysfunction as an adverse event, that a switch to tiagabine monotherapy for 14 weeks statistically and clinically reduced antidepressant-induced sexual dysfunction. The ASEX scores were reduced by approximately 25% which subjects reported as clinically relevant and helpful.

In addition, tiagabine appeared to maintain the response from symptoms of GAD that had been achieved while subjects were on their original SSRI/SNRI regimen. There was no apparent worsening beyond pre-tiagabine baseline in anxiety symptoms. While these results are encouraging, the findings should be interpreted with caution in light of several limitations of this study, including the small sample size, the lack of a placebo control and the lack of a cross-over design. In addition, the ASEX has received only limited use as a research tool and so a degree of caution should be employed when comparing the results of these analyses with those obtained using other measures of sexual functioning (27). The authors could not measure subjects' pre-SSRI/SNRI baseline level of sexual functioning for longitudinal comparison, but relied on subject self-report of sexual difficulty immediately following SSRI/SNRI initiation. The initial improvement in GAD and depressive symptoms could represent positive anxiolytic response acceleration, improvement, or placebo effect. There is a subtle return noted towards subjects' baseline SSRI/SNRI treatment HAM-A and HADS scores and ultimate tiagabine maintenance outcome might require a longer term study of 6–12 months to see if efficacy is continued or not. Per the hypotheses of the study, the authors felt that tiagabine would be a reasonable and equal substitute for SSRI/SNRI with less sexual adverse effects and that a 14-week period would be enough to detect GAD relapse.

The findings reported here are consistent with previous studies of tiagabine in subjects with GAD. In a small, 10-week, open-label study of tiagabine (4–16 mg/day) using the SSRI paroxetine (20–40 mg/day) as a positive control, tiagabine was shown to be at least as effective as paroxetine in significantly reducing anxiety and comorbid depressive symptoms (21). In addition, both agents improved sleep quality, overall clinical condition and subject functioning. While both tiagabine and paroxetine were generally well tolerated, paroxetine reduced sexual functioning in both men and women, as assessed by the Derogatis Interview for Sexual Functioning. In contrast, tiagabine significantly improved female sexual functioning (p < 0.05 versus baseline) and did not impact male sexual functioning (21). Interestingly, paroxetine has been associated with somewhat higher reported rates of sexual dysfunction than other SSRIs (27).

A recent randomized, double-blind, placebo-controlled study evaluated tiagabine (4–16 mg/day) in 266 subjects with GAD (22). Tiagabine significantly reduced symptoms of GAD according to the observed case and mixed models repeated-measures analyses, with a significant reduction in HAM-A total score occurring as early as week 1 compared with placebo (p < 0.05). Sexual functioning, assessed using the Massachusetts General Hospital Sexual Functioning Questionnaire, was not adversely affected following tiagabine, as there was no difference compared with placebo in the mean change in scores from baseline. Similar to the findings of the current study, tiagabine was not associated with a worsening of depressive symptoms (22). Rather, there was a trend towards improvement as shown by the mean reduction in baseline Montgomery-Asberg Depression Rating Scale score.

Studies investigating antidepressant-associated sexual dysfunction have largely been conducted in subjects with major depressive disorder. These have shown that medications with predominantly serotonergic effects, such as the SSRIs, have generally been associated with higher rates of treatment-emergent sexual dysfunction. Furthermore, results show a significantly greater impairment of sexual functioning in men compared with women (27,28). The current study did not distinguish between male and female subjects, although such an analysis could be performed with larger cell sizes.

In the absence of guidelines to inform clinicians how to manage those with antidepressant-induced sexual dysfunction, a number of published studies are available that compare rates of sexual dysfunction following treatment. These suggest that switching to an alternative antidepressant such as bupropion and possibly mirtazapine, whose pharmacological profiles differ from that of the SSRIs, results in lower rates of sexual impairment (10,29–31). Another strategy involves using an antidepressant with the ability to obtain a satisfactory clinical response at a relatively low dose, such as escitalopram (32), while some studies suggest using an agent such as sildenafil to overcome antidepressant-induced erectile dysfunction (33). Tiagabine, an SGRI, has a pharmacological profile different to that of the currently available antidepressants. A direct comparison cannot be made between the results of this study and others investigating sexual dysfunction due to the different assessment scales used and the different populations being studied. However, it would be useful to perform controlled, comparative studies, to determine how tiagabine performs in improving treatment-induced sexual dysfunction in relation to the other antidepressants.

Tiagabine was reasonably tolerated in this study, though it is noted that about one-third of subjects withdrew. The initial rapid dose titration utilized in this study did cause several subjects to withdraw from the study due to commonly reported adverse events. Some of these withdrawals may have been attributable to serotonin discontinuation syndrome despite clinical tapering of SSRI/SNRI in at least two subjects. Interestingly, a majority of the subjects who discontinued tiagabine because of adverse events showed a decrease in symptoms of anxiety and alleviation of their sexual dysfunction, but felt their adverse events were not acceptable enough for them to continue. A less aggressive dosing regimen in future studies may avoid the limitations of tolerability while maintaining the current level of symptoms of GAD afforded by SSRI/SNRI and at the same time ensuring a return of sexual functioning.

CONCLUSIONS

The pilot results presented here suggest that the SGRI tiagabine may be a useful alternative as monotherapy for the alleviation of sexual adverse events in subjects with GAD previously receiving SSRI/SNRI. Additional controlled, dose-finding studies in larger populations may be used to elaborate on these preliminary findings at a better tolerated dose.

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