Annals of Clinical Psychiatry, 17[3]:167–172, 2005

ISSN: 1040-1237 print / 1547-3325 online
DOI: 10.1080/10401230591002138

Taylor & Francis

An Open-label Study of Tiagabine as Augmentation Therapy for Anxiety

THOMAS L. SCHWARTZ, NOUMAN AZHAR, JUHI HUSAIN, NIKHIL NIHALANI, MIHAI SIMIONESCU, DOUGLAS COOVERT, SHEFALI JINDAL, and SYED TIRMAZI

Department of Psychiatry, SUNY Upstate Medical University, Syracuse, NY, USA

Background. *At least 50% of patients with anxiety disorders experience only partial response to pharmacotherapy and require augmentation therapy. Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the CNS, and agents that modulate GABA neurotransmission have shown promise in the treatment of anxiety disorders and are often used as augmentation agents.*

Objective. *This study evaluated tiagabine, a selective GABA reuptake inhibitor (SGRI), as augmentation therapy.*

Methods. *This 8-week, open-label study enrolled patients who remained symptomatic despite adequate drug trials for treatment of anxiety symptoms. Tiagabine augmentation therapy was initiated at 4 mg/d (taken in 2 doses; one in the morning with breakfast and one in the evening with a snack) for 2 days and increased to 8 mg/d for 10 days. Dose was then adjusted according to efficacy/tolerability in increments of 2 mg every 3 days up to a maximum of 20 mg/d. Effect was assessed using the Hamilton Rating Scale for Anxiety (HAM-A), Beck Anxiety Inventory (BAI), Clinical Global Impression (CGI) scale, Pittsburgh Sleep Quality Index (PSQI), and 36-item Short-Form Health Survey (SF-36).*

Results. *Of the 18 patients enrolled, 17 were included in the efficacy analysis; one withdrew due to an adverse event prior to post-baseline assessment. Mean final dose of tiagabine was 13 mg/d. Tiagabine as augmentation therapy further reduced anxiety symptoms, as shown by significant decreases in mean HAM-A total and BAI scores at Week 8 ($P<0.001$). Thirteen patients (76%) responded (≥50% reduction in HAM-A total score), and 10 patients (59%) achieved remission (HAM-A total score ≤7) at Week 8. Tiagabine improved sleep quality, with a significant reduction seen in PSQI global score at Week 8 ($P=.001$). Augmentation therapy with tiagabine was generally well tolerated.*

Conclusion. *These preliminary findings suggest that the SGRI tiagabine may be an effective and generally well tolerated augmentation therapy in patients with anxiety who remain symptomatic despite adequate drug trials for treatment of anxiety symptoms.*

Keywords γ-aminobutyric acid (GABA), Selective GABA reuptake inhibitor (SGRI), Tiagabine, Augmentation therapy, Anxiety

INTRODUCTION

Anxiety disorders are one of the most common and disabling forms of psychiatric illness in clinical practice, with an estimated lifetime prevalence of 25% in the U.S. (1). The most common anxiety disorders are social anxiety disorder (SAD), posttraumatic stress disorder (PTSD), generalized anxiety disorder (GAD), and panic disorder (PD). These are characterized by a diverse range of physiological and psychological symptoms and triggering events. Often, the emotional arousal that characterizes anxiety is an adaptive behavior that may offer protection from stressful events. When the amplitude or frequency of anxiety increases it becomes pathological, causes distress and interferes with daily functioning.

Selective serotonin reuptake inhibitors (SSRIs) are the most commonly used pharmacotherapies in the treatment of anxiety (2). The efficacy of SSRIs is well documented; however, not all patients are able to tolerate these agents (adverse events include insomnia, weight gain, and sexual dysfunction), and not all patients respond fully to an adequate trial (i.e., achieve remission) of serotonergic drug therapy (3,4). Treatment options in patients who do not achieve remission include increasing the dose of current therapy, switching to an alternative anxiolytic agent, or augmenting with a drug targeting a different neurotransmitter system.

Gamma-aminobutyric acid (GABA), the predominant inhibitory neurotransmitter in the central nervous system, plays a

Address correspondence to Thomas L. Schwartz, Department of Psychiatry, SUNY Upstate Medical University, 750 East Adams Street, Syracuse, NY 13210, USA. E-mail: schwartzresearch1@yahoo.com

central role in the pathogenesis and treatment of anxiety disorders (5,6). Results of neuroimaging studies in patients with GAD, PD, and PTSD show alterations in the GABA system in areas of the brain linked to anxiety disorders (7,10). GABA-modulating drugs, such as barbiturates and benzodiazepines, have been used to effectively treat many symptoms of anxiety. These classes of medication are, however, prone to misuse and addiction and have been delegated to second-line therapy to the SSRIs.

Tiagabine is a selective GABA reuptake inhibitor (SGRI) that increases synaptic GABA availability via selective inhibition of the GAT-1 GABA transporter (11,12). This medication is currently FDA-approved for adjunctive therapy in adults and children 12 years and older in the treatment of partial seizures with the presumed anti-seizure mechanism related to SGRI action and increased inhibitory GABA tone that dampens neuronal firing. This elevation of GABA tone is related to the increased availability of endogenous GABA. This is unlike the benzodiazepine class of anti-epileptic and sedative-hypnotic agents that elevate GABA tone by directly stimulating the GABA-A receptor, thus facilitating more inhibitory chloride ion influx into neurons. This direct receptor modulation may explain tolerance and dependence to this class of drugs. Tiagabine does not share this potential adverse effect. There are no known end organ side effects and laboratory monitoring is not needed. Typical acute side effects include: nausea, headache, dizziness, fatigue and somnolence. These are often transient and are mitigated when taken orally with food (13). Rare cases of seizure induction have been reported.

In a randomized, positive-controlled, open-label study in patients with GAD, both tiagabine and paroxetine monotherapy significantly reduced symptoms of GAD and improved overall clinical condition (14). As the pharmacokinetic profile of tiagabine has a low potential for interaction with concomitant drug therapy and is known to facilitate GABA activity pharmacodynamically (15), tiagabine may also be a promising augmentation therapy for anxious patients. This study evaluated tiagabine as augmentation therapy in patients who remained symptomatic despite adequate drug trials for treatment of anxiety symptoms.

MATERIALS AND METHODS

This was an 8-week, single-center, open-label study. The study design was approved by the local institutional review board, and all patients provided written informed consent to participate.

Patients

Male and female outpatients (aged 18 to 65 years) with a diagnosis of any anxiety disorder (except OCD) (16) according to the *Diagnostic and Statistical Manual of Mental Disorders* Fourth Edition (DSM-IV), a rating of at least "moderately ill" (score of ≥4) on the Clinical Global Impression of Severity (CGI-S) scale for anxiety (17), and who all remained symptomatic despite an clinically adequate trial of drug therapy for anxiety symptoms were eligible for inclusion in this trial. Adequate treatment duration for current anxiety medication was considered to be 4 weeks at the maximum recommended or tolerated dosage. Inadequate response was defined as less than 50% improvement in anxiety symptoms, as measured subjectively by patients or objectively by physicians.

Patients were excluded from the trial if they had a diagnosis of any active primary psychiatric disorder other than anxiety, active substance abuse within 6 months of study entry, a history of suicidal tendencies, cognitive behavioral therapy within 28 days of study entry, or any other medical condition or medication that was likely to interfere with assessment of tiagabine response. OCD patients were not eligible as they tend not to respond to GABA drugs. Most patients were taking serotonergic anxiolytic agents.

Treatment

Current drug therapy was maintained at a constant dose throughout the study. Tiagabine as augmentation therapy was initiated at a dose of 4 mg/d for the first 2 days and then increased to 8 mg/d for the following 10 days. The tiagabine dose was then individually adjusted according to efficacy/tolerability in increments of 2 mg every 3 days, with a maximum increase of 4 mg/week. The maximum permitted total daily dose of tiagabine was 20 mg. Total daily doses of tiagabine were taken as two doses, one in the morning with breakfast and one in the evening with a snack. Evening dose was allowed to be increased preferentially in some patients due to daytime adverse events.

Assessments

Assessments were made at baseline, weeks 3, 5 and 7, and at the end of the study. Efficacy was assessed using the clinician-rated Hamilton Rating Scale for Anxiety (HAM-A) (18), Beck Anxiety Inventory (BAI) (19), and Clinical Global Impression of Change (CGI-C) scale (18). Sleep quality was evaluated using the Pittsburgh Sleep Quality Index (PSQI), a subjective, 7-component scale (score range 0–21) where a score of >5 is suggestive of significant sleep disturbance (20). Patient functioning was monitored at baseline and weeks 5 and 8 using the 36-item Short-Form Health Survey (SF-36) (21). Adverse events were recorded throughout the study by way of verbal report and use of the UKU side effect rating scale (22).

Statistics

Patients with at least one post-baseline efficacy measurement were evaluated for efficacy using last-observation-carried-forward

(LOCF). All patients who received at least one dose of study medication were evaluated for safety (intent-to-treat population). Descriptive statistics were calculated for each assessment parameter. Changes from baseline in mean scores on the HAM-A, BAI, PSQI, and SF-36 at each study visit were compared using the paired Student's t-test or Wilcoxon signed rank test. Changes in CGI-C ratings between visits were compared using the Wilcoxon signed rank test. All statistical tests were two-tailed, with a significance level of 0.05. Treatment response was defined as a reduction of ≥50% in HAM-A total score. Remission was defined as HAM-A total score of ≤7 at endpoint (20).

RESULTS

Demographics and Clinical Characteristics

Patient demographics and clinical characteristics at baseline are summarized in Table 1. The most common diagnosis in this study population was GAD, which was noted in 10 patients (56%). The majority of patients (14 patients; 78%) were receiving SSRIs for treatment of anxiety symptoms at the time of study enrollment, with paroxetine and citalopram (n=6 and n=5, respectively) being the most common SSRIs. Others utilized benzodiazepines. Eighteen patients were enrolled and received study medication, of which 17 were evaluable for efficacy and comprised the intent-to-treat population, for whom missing data were estimated by a last-observation carried forward (LOCF) technique. The other patient discontinued treatment because of a panic attack, which was considered unlikely related to study medication, on day 9 prior to follow-up assessment. Of the 17 patients included in the efficacy analysis, reasons for withdrawal included adverse events (n=1; week 1) and loss to follow-up (n=2; both at week 4). The final mean dose of tiagabine was 13 mg/d (range 2–20 mg/d), divided between a morning and evening dose.

Table 1 Patient Demographics and Clinical Characteristics at Baseline

Characteristic[a]	**Tiagabine (N=18)**
Age (years)	38 (26–53)
Gender, n (%)	
Male	7 (39%)
Female	11 (61%)
Duration of anxiety (years)	9 (0–31)
Age at time of initial diagnosis (years)	29 (19–44)
Current anxiety medication, n (%)	
SSRI	14 (78%)
Venlafaxine	2 (11%)
Nefazodone	1 (6%)
Alprazolam	1 (6%)
Diagnosis, n (%)[b]	
Generalized anxiety disorder	10 (56%)
Panic disorder	8 (44%)
Posttraumatic stress disorder	4 (22%)
Social anxiety disorder	3 (17%)
CGI-S rating, n (%)	
Mildly/moderately ill	15 (83%)
Markedly/severely ill	3 (17%)

[a]Values are expressed as mean (range) unless otherwise stated.
[b]More than one indication for anxiety medication was given in some patients.
SSRI, selective serotonin reuptake inhibitor; CGI-S, Clinical Global Impression of Severity.

Effectiveness of Tiagabine as Augmentation Therapy

Tiagabine as augmentation therapy further reduced symptoms of anxiety, as shown by significant reductions from baseline in mean HAM-A total scores (Figure 1), as well as HAM-A psychic and somatic anxiety subscale scores (Table 2). Onset of tiagabine activity was observed at Week 3, the first study visit (Figure 1). Thirteen patients (76%) were treatment responders (≥50% reduction in HAM-A total score at endpoint), and 10 patients (59%) achieved remission (HAM-A total score ≤7 at endpoint) (Figure 2). Consistent with HAM-A results, tiagabine reduced mean scores on the BAI (Table 2), with improvements from baseline seen at each time point ($P \leq 0.002$). Eighty-eight percent (n=15) of patients had a positive clinical response to tiagabine as augmentation therapy, as measured by ratings of much or very much improved on the CGI-C at week 8.

Augmentation with tiagabine improved sleep quality, as shown by the significant reduction in PSQI global score ($P=0.001$; Table 2). In addition, a reduction in HAM-A insomnia item score was also noted ($P=0.002$ at week 8 versus baseline). Improvements in SF-36 mental and physical composite scores were observed at week 8, though the change from baseline was not significant.

Tolerability

Tiagabine augmentation therapy was generally well tolerated; cognitive slowing (a nonCOSTART, more clinically, descriptive term where subjects felt their thought processes were slowed) was the most common adverse event occurring in 8 patients (44%; Table 3). These adverse events were mild or moderate in severity, with no serious adverse side effects reported. Side effects where often transient and remitted. Two patients withdrew from the study due to adverse events, one due to a panic attack and the other due to headache and cognitive slowness.

DISCUSSION

In this 8-week, open-label study, augmentation therapy with tiagabine (mean dose 13 mg/d) further reduced symptoms of anxiety and improved sleep quality. These effects were apparent

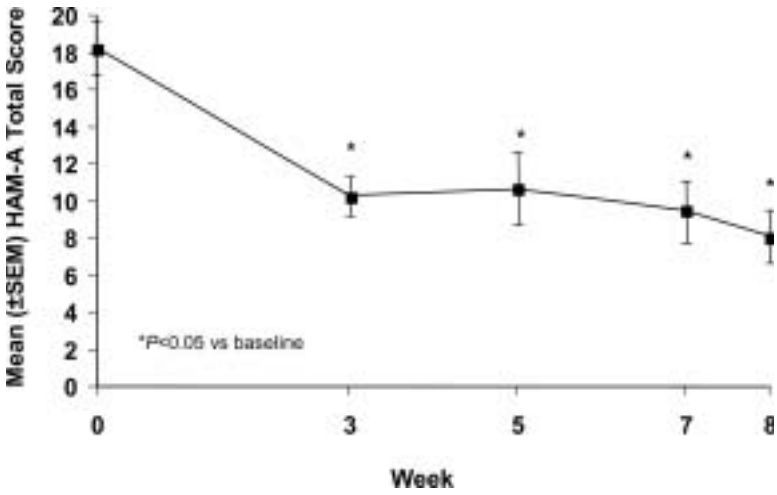

Figure 1 Change in mean HAM-A total score during augmentation therapy with tiagabine.

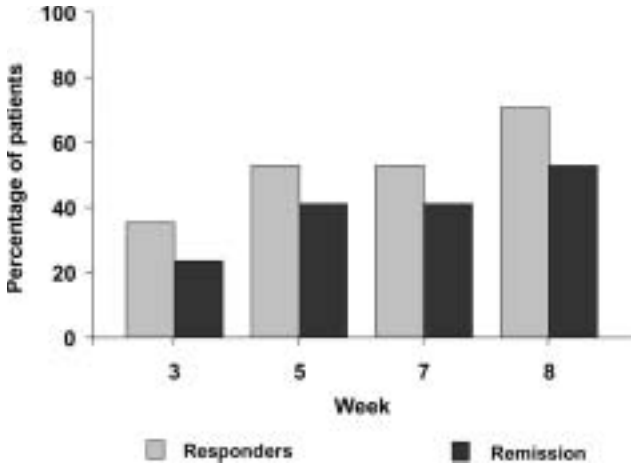

Figure 2 Percentage of patients rated as treatment responders (reduction of ≥50% in HAM-A total score) and those achieving remission (HAM-A total score ≤7) during augmentation therapy with tiagabine.

Table 2 Mean (SEM) Scores on Assessment Scales at Baseline and After 8 Weeks of Augmentation Therapy with Tiagabine

	Tiagabine (N=17)	
Assessment Scale	Baseline	Week 8
HAM-A		
Total	18.2 (1.4)	8.1 (1.3)[a]
Psychic anxiety subscale	11.6 (1.0)	6.1 (1.0)[a]
Somatic anxiety subscale	6.6 (0.7)	2.0 (0.5)[a]
BAI		
Total	19.2 (3.4)	10.1 (2.8)[a]
PSQI		
Global	11.2 (1.2)	7.6 (1.2)[a]

[a]P < 0.01 versus baseline.

Table 3 Most Common Treatment-emergent Adverse Effects Reported During Augmentation Therapy with Tiagabine (>10%)

	Tiagabine (N=18)	
Adverse Event	N	%
Cognitive slowing[a]	8	44
Somnolence	4	22
Headache	2	11
Insomnia	2	11
Rash	2	11
Flu syndrome	2	11
Elevated SGPT	2	11

SGPT, serum glutamic pyruvic transaminase.
[a]COSTART term substituted with a more clinically descriptive term.

at the time of the first assessment (3 weeks) and maintained throughout the 8 weeks of therapy. Overall, 76% of patients were considered to be treatment responders, and 59% of patients achieved remission after 8 weeks of tiagabine as augmentation therapy. Tiagabine was generally well tolerated, with one patient discontinuing therapy due to an adverse event. No reports of serious advents events were noted. The observed tolerability profile was consistent with the known safety profile of tiagabine (21).

These effects of tiagabine in the treatment of anxiety in this study are in keeping with preliminary reports in the literature. In a randomized, open-label trial study in patients with GAD, tiagabine (10 mg/d) and the positive control paroxetine (27 mg/d) significantly reduced symptoms of GAD and improved overall clinical condition (13). In case reports, tiagabine (2–16 mg/d), as monotherapy or augmentation therapy, reduced symptoms of anxiety in patients with GAD, PTSD, and PD (22–24). The response to tiagabine with regard to subjective sleep quality in the current study is also consistent with earlier observations, where tiagabine increased self-perceived sleep intensity and

improved objective sleep quality in healthy elderly subjects in a double-blind, placebo-controlled study (25).

The clinical effect of tiagabine observed here may be anticipated based on the current understanding of the role of the GABA system in the pathophysiology of anxiety (5,6) and sleep disorders/disturbances (26). The effectiveness of tiagabine as augmentation of SSRI therapy would be expected given that both neurotransmitters regulate the neuroanatomical circuits mediating fear in anxiety disorders (5). Therefore, combination therapy with agents that selectively target the GABA and serotonergic systems may provide synergistic therapeutic effects and better alleviate anxiety than monotherapy alone (27), as suggested by the results of this study.

Interpretation of the results of this trial must consider the open-label design, small number of patients, and heterogeneity of the patient population in terms of primary anxiety disorder and current treatment. We, therefore, cannot comment on relative effectiveness between anxiety disorders due to lack of adequate sample size. However, the enrollment of a diverse patient population may actually better translate to typical clinical practice. Another limitation may have been that the entry criterion for adequate treatment duration was greater than 4 weeks; however, with the exception of one patient whose previous treatment duration was 32 days, all others had durations of at least 56 days. Moreover, as therapeutic response was not monitored on primary treatment, it is not possible to determine whether the patients entering this study were partial responders or complete nonresponders, though all clearly required further treatment for their anxiety symptoms. In clinical practice, this SGRI seems to achieve symptom response faster than the SSRIs, but slower than the benzodiazepines. Our study's first follow-up visit did not allow us to evaluate symptom response at weeks one or two.

CONCLUSION

These preliminary findings suggest that the SGRI tiagabine may be an effective and generally well tolerated augmentation therapy in patients with anxiety who remain symptomatic despite adequate drug trials for treatment of anxiety symptoms. Further study of tiagabine in this setting is warranted. At the CINP, data relating to a randomized, placebo-controlled, statistically powered study where monotherapy Tiagabine was utilized to treat GAD revealed a significant lowering of anxiety symptoms (28). It is hoped that replication studies will follow en route to potential FDA review.

ACKNOWLEDGMENTS

This work was supported by Cephalon, Inc., West Chester, PA, and presented at the American Psychiatric Association Annual Meeting, 17-22 May 2003, San Francisco, CA.

REFERENCES

1. Kessler RC, McGonagle KA, Zhao S et al.: Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Arch Gen Psychiatry* 1994; 51:8–19
2. Bandelow B, Zohar J, Hollander E et al.: World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders. *World J Biol Psychiatry* 2002; 3:171–199
3. Ballenger JC: Overview of different pharmacotherapies for attaining remission in generalized anxiety disorder. *J Clin Psychiatry* 2001; 62(suppl 19):11–19
4. Pollack MH, Zaninelli R, Goddard A et al.: Paroxetine in the treatment of generalized anxiety disorder: Results of a placebo-controlled, flexible-dosage trial. *J Clin Psychiatry* 2001; 62:350–357
5. Ninan PT: The functional anatomy, neurochemistry, and pharmacology of anxiety. *J Clin Psychiatry* 1999; 60(suppl 22):12–17
6. Nutt DJ, Malizia AL: New insights into the role of the $GABA_A$-benzodiazepine receptor in psychiatric disorder. *Br J Psychiatry* 2001; 179:390–396
7. Tiihonen J, Kuikka J, Rasanen P et al.: Cerebral benzodiazepine receptor binding and distribution in generalized anxiety disorder: a fractal analysis. *Mol Psychiatry* 1997; 2:463–471
8. Malizia AL, Cunningham VJ, Bell CJ et al.: Decreased brain $GABA_A$-benzodiazepine receptor binding in panic disorder: Preliminary results from a quantitative PET study. *Arch Gen Psychiatry* 1998; 55:715–720
9. Bremner JD, Innis RB, White T et al.: SPECT [I-123]iomazenil measurement of the benzodiazepine receptor in panic disorder. *Biol Psychiatry* 2000; 47:96–106
10. Goddard AW, Mason GF, Almai A et al.: Reductions in occipital cortex GABA levels in panic disorder detected with 1h-magnetic resonance spectroscopy. *Arch Gen Psychiatry* 2001; 58:556–561
11. Fink-Jensen A, Suzdak PD, Swedberg MD et al.: The gamma-aminobutyric acid (GABA) uptake inhibitor, tiagabine, increases extracellular brain levels of GABA in awake rats. *Eur J Pharmacol* 1992; 220:197–201
12. Borden LA, Murali Dhar TG, Smith KE et al.: Tiagabine, SK&F 89976-A, CI-966, and NNC-711 are selective for the cloned GABA transporter GAT-1. *Eur J Pharmacol* 1994; 269:219–224
13. Suzdak PD, Jansen JA: A review of the preclinical pharmacology of tiagabine: A potent and selective anticonvulsant GABA uptake inhibitor. *Epilepsia* 1995; 36(6):612–626
14. Rosenthal M: Tiagabine for the treatment of generalized anxiety disorder: A randomized, open-label, clinical trial with paroxetine as a positive control. *J Clin Psychiatry* 2003; 64:1245–1249
15. Adkins JC, Noble S: Tiagabine. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in the management of epilepsy. *Drugs* 1998; 55:437–460
16. American Psychiatric Association: Anxiety disorders. In: *Diagnostic and Statistical Manual of Mental Disorders,* , Text Revision. 4th. Washington, DC: American Psychiatric Association, 2000:429–484
17. Guy W.: Clinical global impression of change (CGI-C) (rating scale). In: *ECDEU Assessment Manual for Psychopharmacology*. Washington, D.C.: National Institute of Mental Health, US Department of Health, Education, and Welfare, 1976
18. Hamilton M: The assessment of anxiety states by rating. *Br J Med Psychol* 1959; 32:50–55

19. Beck AT, Epstein N, Brown G et al.: An inventory for measuring clinical anxiety: psychometric properties. *J Consult Clin Psychol* 1988; 56:893–897
20. Buysse DJ, Reynolds CF, 3rd, Monk TH et al: The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989; 28:193–213
21. Ware JE, Jr., Sherbourne CD: The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992; 30:473–483
22. Lingjaerde O, Ahlfors UG, Bech P, et al: The UKU Side Effect Rating Scale: A new comprehensive rating scale for psychotropic drugs, and a cross-sectional study of side effects in neuroleptic-treated patients. *Acta Psychiatr Scand Suppl* 1987; 76:1–100
23. Ballenger JC: Clinical guidelines for establishing remission in patients with depression and anxiety. *J Clin Psychiatry* 1999; 60(suppl 22):29–34
24. Leppik IE, Gram L, Deaton R et al.: Safety of tiagabine: Summary of 53 trials. *Epilepsy Res* 1999; 33:235–246
25. Berigan T: Treatment of posttraumatic stress disorder with tiagabine. *Can J Psychiatry* 2002; 47:788
26. Schwartz TL: The use of tiagabine augmentation for treatment-resistant anxiety disorders: a case series. *Psychopharmacol Bull* 2002; 36:53–57
27. Crane D: Tiagabine for the treatment of anxiety. *Depress Anxiety* 2003; 18:51–52
28. Van Ameringen M, Pollack MH, et al. Poster presented at CINP, 2004