Open-Label Tiagabine Monotherapy for Major Depressive Disorder With Anxiety

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Objective: Gamma-aminobutyric acid (GABA) plays a key role in the pathophysiology and treatment of depression and anxiety. Tiagabine, a selective GABA reuptake inhibitor (SGRI) that enhances normal GABA tone, was evaluated for its efficacy and safety in the treatment of depression comorbid with significant anxiety.

Method: In this 8-week, single-center, open-label study, adults with DSM-IV–diagnosed major depressive disorder and significant anxiety (i.e., "anxious depression") received tiagabine monotherapy, initiated at 4 mg/day and titrated for optimum response as tolerated to a maximum dose of 20 mg/day. Symptoms, function, and adverse events were assessed at regular intervals. Patients were entered from April 2002 to February 2003.

Results: Nineteen patients entered the study and 15 met criteria for intent-to-treat analyses. Of those, 6 (40%) discontinued treatment and 9 (60%) completed the 8-week protocol. Tiagabine significantly improved depression, as shown by a reduction in mean ± SD Hamilton Rating Scale for Depression scores from baseline (31.9 ± 6.1) to endpoint (17.0 ± 12.4; p = .002). Categorical response rate was 47% (N = 7). Tiagabine also significantly improved anxiety (Hamilton Rating Scale for Anxiety baseline score of 22.7 ± 4.9 vs. endpoint score of 12.5 ± 8.8; p = .002). The mean ± SD final daily dose was 12.8 ± 5.8 mg. The most commonly reported adverse events were dizziness, headache, and gastrointestinal upset/nausea.

Conclusion: These results suggest the potential of the SGRI tiagabine in the treatment of depression with anxiety. Large, placebo-controlled trials are needed.

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This material concerns an indication for tiagabine (Gabitril) that has not been reviewed by the U.S. Food and Drug Administration.

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Although the monoamine theory of major depression is now considered too limited to fully explain the etiology of the disorder, our understanding of the physiologic mediators of mood remains rudimentary. Elucidating the key functions and critical interrelationships of the "older" and "newer" neurotransmitters involved in depression continues to command the attention of investigators in this field. One area of emerging interest is the functioning of γ-aminobutyric acid (GABA) neurons and their potential role in modulating mood states. While the role of GABA in anxiety has been known for decades,[1–3] several converging lines of preclinical and clinical research suggest that GABA-mediated inhibitory systems have an important role in depression as well.[4–6]

The GABAergic theory of mood disorders can be traced back to Emrich and colleagues,[7] who explored the antimanic effects of valproate, an anticonvulsant with GABAergic properties. Since that publication, there has been extensive work on GABA function in depressive illness, with clinical studies demonstrating that GABA levels are significantly decreased in the plasma[5,8–12] and cerebrospinal fluid[13–17] of unipolar depressed patients. More recently, Sanacora and colleagues[18,19] have documented lower GABA levels in the occipital cortex of medication-free depressed patients compared to healthy controls using magnetic resonance spectroscopy. Furthermore, stud-

ies have shown increased cortical GABA concentrations after successful electroconvulsive therapy[20,21] or selective serotonin reuptake inhibitor (SSRI) treatment for unipolar depression.[22]

Tiagabine is a selective GABA reuptake inhibitor that enhances normal GABA tone at all GABA receptors.[23–25] Tiagabine is currently approved by the U.S. Food and Drug Administration for the treatment of partial complex seizures and appears safe and well tolerated in that patient population.[26,27] Tiagabine monotherapy was shown to improve emotional and interpersonal adjustment and mood in a cohort of 123 patients with uncontrolled partial seizures[28] and to promote slow wave sleep in a sample of 10 healthy volunteers.[29] The anxiolytic properties of tiagabine have shown promise in a number of case reports and preliminary studies of posttraumatic stress disorder,[30–32] panic disorder,[33] and generalized anxiety disorder.[31,34–36]

There is limited clinical experience with tiagabine for the treatment of primary mood disorders. While tiagabine did not show efficacy in the treatment of acute mania,[37] 2 case reports[38,39] and 1 open case series[40] documented improvement in mood stability in patients with bipolar disorder. However, these results were not replicated in a second case series.[41]

In light of the growing knowledge base regarding GABA-related central nervous system correlates in affective illness and the established anxiolytic properties of GABAergic agents,[42,43] we undertook a prospective, open-label pilot study of tiagabine in a cohort of depressed outpatients with prominent anxiety (i.e., "anxious depression" subtype). Patients with anxious depression have been reported to comprise nearly half of all depressed patients seeking treatment in a large multicenter study.[44] Specific clinical and sociodemographic variables characterize depressed patients with high levels of anxiety, lending support for the notion that anxious depression is a common and distinct subtype.[44] To our knowledge, there are no published reports describing tiagabine use in this population.

METHOD

Subjects

The sample consisted of 19 outpatients with a DSM-IV diagnosis of major depressive disorder (MDD) with significant concurrent anxiety. Inclusion criteria were age between 18 and 65 years, a current and primary DSM-IV[45] diagnosis of MDD according to the Mini-International Neuropsychiatric Interview,[46] a Hamilton Rating Scale for Depression (HAM-D, 28-item)[47–49] score > 17, and a Hamilton Rating Scale for Anxiety (HAM-A)[50] score > 14. Patients were excluded if they had a clinically significant medical condition or if they required medication that would interfere with the interpretation of the study, such as benzodiazepines, phenobarbital, valproate, gabapentin, topiramate, lamotrigine, or other antiepileptic drugs. In addition, patients were excluded if a detailed history revealed substance abuse within the past year or if a urine toxicology screen was positive during pre-enrollment evaluation. Eligible patients were free of mood medications for at least 14 days (28 days for fluoxetine) prior to enrollment. The trial was conducted in the Mood Disorders Research Clinic (outpatient) at Butler Hospital, a free-standing psychiatric hospital affiliated with Brown Medical School. The Butler Hospital Institutional Review Board approved the protocol, and all patients gave voluntary written informed consent to participate. Patients were enrolled from April 2002 to February 2003.

Measures

Depression and anxiety symptoms and overall function were evaluated using the HAM-D, the HAM-A, the Inventory for Depressive Symptomatology-Self-Report version (IDS-SR),[51,52] and the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q).[53] In addition, the Clinical Global Impressions (CGI)[54] scales for change (CGI-C) and severity of illness (CGI-S) were completed at each visit. Additional scales were used to assess sleep disturbances (the Pittsburgh Sleep Quality Index; PSQI)[55] and work activities (the Work Productivity and Activity Impairment Questionnaire; WPAI).[56] Adverse events, elicited by direct verbal query and spontaneous report, were noted at each visit and reported by symptom duration, severity, and presumptive relation to study medication.

Procedure

After initial screening, patients who met eligibility criteria were invited to participate in this 8-week, open-label study of tiagabine monotherapy. After a detailed psychiatric and medical history, the subjects had a medical work-up including a complete physical and neurologic examination, electrocardiography, serum chemistries including thyroid and liver function tests, and urine toxicology for drugs of abuse. Women of childbearing potential had urine pregnancy tests at study inception and used 2 forms of medically accepted birth control throughout the trial.

After the baseline evaluation, patients returned weekly for the first 4 weeks, then biweekly (once every 2 weeks) for weeks 5 through 8. The CGI, HAM-D, HAM-A, IDS-SR, and Q-LES-Q were administered at each visit by trained clinicians. The PSQI and WPAI were evaluated at baseline, week 4, and at the week 8 endpoint.

Tiagabine was initiated at 4 mg daily in 2 divided doses. Dose increases were individually titrated to patient response and side effects in 2- to 4-mg per week

Table 1. Clinical Characteristics of Patients Treated With Tiagabine for Major Depressive Disorder With Significant Anxiety (N = 15)

Clinical Characteristic	Value
Age, mean ± SD (range), y	47.8 ± 6.4 (39–61)
Gender, N (%)	
Male	6 (40)
Female	9 (60)
Weight, mean (range), lb	154 (94–221)
Diagnoses, N (%)	
Major depressive disorder (unipolar)	15 (100)
Melancholic subtype	9 (60)
Secondary anxiety disorder	4 (27)
Social phobia	2 (13)
Generalized anxiety disorder	2 (13)
Panic disorder	2 (13)
Clinical Global Impressions-Severity of Illness scale, N (%)	
Moderate	8 (53)
Marked	7 (47)

Table 2. Outcome Measures in Open-Label Tiagabine Trial Among Patients With Major Depressive Disorder and Significant Anxiety[a]

Outcome Measure	Baseline (N = 15)	Endpoint (N = 15)	p Value (2-tailed)
Categorical response, N (%)			
Responder	…	7 (47)	…
Nonresponder	…	8 (53)	…
Remission (HAM-D-17 score ≤ 7), N (%)	…	5 (33)	…
Depressive symptoms (HAM-D total score)	31.9 (6.1)	17.0 (12.4)	.002
Anxiety symptoms (HAM-A total score)	22.7 (4.9)	12.5 (8.8)	.002
Self-report depressive symptoms (IDS-SR total score)	39.1 (10.1)	22.9 (15.0)	.0004
Global severity of illness (CGI-S score; range, 1–7)	4.5 (0.5)	2.9 (1.6)	.003
Sleep quality (PSQI global score)	10.4 (3.8)	8.6 (4.9)	.10
Work productivity (WPAI score)			
Percentage overall (work)	67.7 (31.2)	79.6 (22.1)	.37
Percentage daily activities	60.0 (34.6)	73.0 (26.4)	.29
Quality of life (Q-LES-Q score)			
Physical health	33.7 (8.8)	40.5 (9.3)	.02
Work	37.2 (14.2)	41.8 (18.0)	.06
Household duties	29.9 (9.2)	36.5 (10.1)	.03
Social relationships	29.6 (8.9)	36.3 (14.0)	.04
General well-being	38.8 (7.2)	47.1 (11.3)	.02
Subjective feelings	39.7 (7.4)	46.7 (13.2)	.09

[a]All values are shown as mean (SD) unless otherwise specified (i.e., categorical response and remission).
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, IDS-SR = Inventory for Depressive Symptomatology-Self-Report, PSQI = Pittsburgh Sleep Quality Index, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire, WPAI = Work Productivity and Activity Impairment Questionnaire.
Symbol: … = no data.

increments, up to a maximum of 20 mg/day. In the absence of significant side effects and clinical benefit, tiagabine dose was further increased at each study visit, with the general goal of achieving symptom relief or highest tolerated dose. Medication adjustments were not allowed during the final 2 weeks of the protocol. Concurrent use of chloral hydrate was only allowed during the first 2 weeks of the study on an as-needed basis for insomnia.

Statistical Analyses

Subjects with at least 1 postbaseline measurement were evaluated for efficacy using last-observation-carried-forward (LOCF) analysis. Comparisons with baseline were made using a 2-tailed paired Student t test with a prior α set at .05. Chi-square tests were used to analyze categorical responses.

Categorical positive response was defined as present when a patient achieved (1) a CGI-C rating of "much improved" or "very much improved" *and* (2) a ≥ 50% reduction in HAM-D total score. Remission was defined as a HAM-D score ≤ 7 (on the core 17 items) or a HAM-A score ≤ 7, with regard to depression and anxiety symptoms, respectively.[57,58] Positive remission status also required that criteria for categorical response be met. Data were analyzed using SPSS software (SPSS for Windows, version 11.5, SPSS, Inc., Chicago, Ill.). Any treatment-emergent side effects rated as "possibly" or "probably" related to tiagabine were counted and described as simple frequencies.

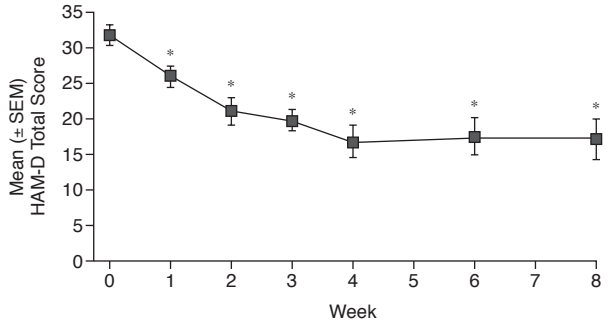
RESULTS

Nineteen patients were enrolled in the study. Of the 4 patients omitted from the intent-to-treat (ITT) analysis, 2 were lost to follow-up after the baseline evaluation and 2 failed to meet entrance criteria (significant medical problem [N = 1] and HAM-A score < 12 [N = 1]). A summary of demographic information (N = 15) is presented in Table 1, and baseline clinical characteristics are presented in Table 2. Systematic data regarding prior treatment trials and treatment resistance were not collected, but all subjects indicated they had undertaken at least 1 lifetime antidepressant medication trial and as such were not fully antidepressant naive.

Six patients in the ITT sample discontinued before completing the 8-week protocol. Three patients withdrew secondary to poor tolerability, 2 due to lack of efficacy, and 1 was withdrawn after a protocol violation (use of a prohibited medication). Baseline characteristics of these patients were not significantly different from those of the group who completed the trial.

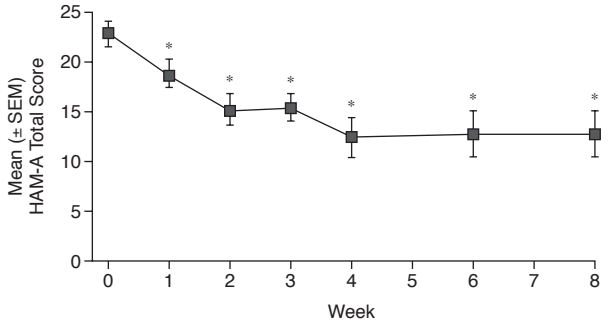
The mean ± SD trial duration was 6.1 ± 1.2 weeks. While 9 patients completed the full 8 weeks of the study, the group that discontinued prematurely remained on the drug for a mean ± SD of 4.8 ± 1.0 weeks. The mean ± SD daily tiagabine dose for the entire group was 12.8 ± 5.8 mg (range, 6–20 mg). The mean ± SD daily dose for completers was 12.6 ± 3.9 mg (range, 8–20 mg), while the

Figure 1. Tiagabine Significantly Reduced Symptoms of Depression Among Patients With Major Depressive Disorder and Significant Anxiety[a]



[a]Mean (± SEM) HAM-D data plotted for intent-to-treat sample, N = 15, last observation carried forward.
*p < .05 versus baseline.
Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

Figure 2. Tiagabine Significantly Improved Symptoms of Anxiety Among Patients With Major Depressive Disorder and Significant Anxiety[a]



[a]Mean (± SEM) HAM-A data plotted for intent-to-treat sample, N = 15, last observation carried forward.
*p < .05 versus baseline.
Abbreviation: HAM-A = Hamilton Rating Scale for Anxiety.

mean ± SD dose of the early termination group was 13.1 ± 4.9 mg/day (range, 6–20 mg). Only 1 subject requested and used chloral hydrate during the first 2 weeks of the protocol.

Tiagabine significantly reduced symptoms of depression across several of the outcome measures (Table 2). The total mean ± SEM HAM-D score decreased from 31.9 ± 6.1 at baseline to 17.0 ± 12.4 at endpoint ($t = 3.7$, $p = .002$; Figure 1). The corresponding mean ± SEM HAM-A scores decreased from 22.7 ± 4.9 to 12.5 ± 8.8 ($t = 3.9$, $p = .002$; Figure 2). The mean CGI-S score decreased from 4.5 to 2.9 at endpoint ($t = 3.6$, $p = .003$).

Self-report assessments reflected a similar improvement. The mean ± SEM IDS-SR score decreased from 39.1 ± 10.1 to 22.9 ± 15.0 ($t = 4.6$, $p = .0004$). Overall functional status also improved, as shown by significant change in the Q-LES-Q domains of "physical health" ($p = .022$), "household duties" ($p = .025$), "social relationships" ($p = .041$), and "general well-being" ($p = .019$). Trend-level improvements were noted in the Q-LES-Q categories of "work" and "subjective feelings" at trial endpoint ($p = .055$ and $p = .087$, respectively). There were no significant changes on the PSQI measure of sleep quality or on work productivity as measured by the WPAI.

A significant negative correlation was found between baseline HAM-D score and magnitude of HAM-D response (percent change from baseline) to tiagabine, suggesting that more severely depressed patients had more benefit from tiagabine ($r = –0.61$, $p = .01$) or possible "basement effects" from some individuals in the lower range of baseline scores. Post hoc analysis confirmed that the statistically significant decrease we observed in mean HAM-D total score persisted after removal of items that assess anxiety.

Seven patients (47%) met categorical response criteria at endpoint. Five (33%) achieved remission with regard to depressive symptoms and 4 (27%) achieved remission of both depressive and anxiety symptoms.

The most common adverse events were dizziness (N = 9, 60%), headache (N = 5, 33%), and gastrointestinal upset/nausea (N = 5, 33%). Three patients (20%) reported treatment-emergent myalgias and 3 (20%) reported sedation. Night sweats and loose stool were each reported by 2 patients (13%). Weakness, muscle twitching, insomnia, flatulence, excessive sweating, and blurred vision were each reported by 1 patient (7%). Three patients (20%) dropped out because of side effects: 1 had headaches, 1 had nausea and gastrointestinal upset, and 1 had a cluster of flu-like symptoms including cervical adenopathy, sore throat, and arthralgias. There were no serious adverse events, and there were no significant changes in weight ($p = .32$).

DISCUSSION

This open-label study in patients with major depressive disorder and concurrent anxiety (i.e., "anxious depression" subtype) showed significant symptom and functional improvement following tiagabine monotherapy over an 8-week period. Consistent improvement was seen in both clinician and patient-rated instruments across all symptom categories. Positive clinical response occurred in 47% of patients, and 33% and 27% of the patients met criteria for remission of depression and anxiety symptoms, respectively. These outcomes are comparable to those reported for active drug in placebo-controlled clinical trials of approved antidepressant drugs,[59] but response rates in open-label studies are typically higher than those observed in studies employing a placebo-controlled design.[60]

Tiagabine responders (N = 7) could be distinguished statistically from nonresponders (N = 8) at week 4 (Figure 1), a time course of improvement that parallels symptom change seen in standard antidepressant trials.[61] The drug was generally well tolerated by the majority of patients, but 20% of our small sample could not tolerate side effects attributed to tiagabine. No patients reported symptoms consistent with new-onset seizure activity, a drug-related risk that has been described in safety information released by the manufacturer of tiagabine in the past year.[62] It should be noted, however, that our sample was too small to test the safety of tiagabine with respect to the risk of new-onset seizure activity. Conclusions regarding tolerability of tiagabine in depression with anxiety await more definitive trials. Additionally, we did not characterize subjects in this pilot study with regard to degree of treatment resistance, so we are unable to speculate about the potential role of tiagabine when other adequate antidepressant trials have failed.

A majority of patients with a primary mood disorder have significant anxiety symptoms at some point during the course of their illness.[63] Furthermore, those suffering from depression with comorbid anxiety symptoms may face a more chronic or disabling course of illness[64,65] and require more medication for optimum symptom control.[66,67] Concurrent use of benzodiazepines and a standard antidepressant is a commonly employed strategy for this patient population, but cognitive side effects, tolerance, and the potential for abuse limit enthusiasm for chronic treatment with benzodiazepines. Selective serotonin reuptake inhibitors are popular first-line treatments for anxious depression, but SSRI-induced sexual dysfunction frequently compromises patient satisfaction with the treatment. Other non-SSRI and nonbenzodiazepine pharmacotherapies for depression with anxiety would be welcome additions to the currently available repertoire. The results we report for tiagabine monotherapy from this small, open-label study are encouraging, but data from larger, placebo-controlled trials are needed[68] to fully delineate the role of tiagabine in the treatment of patients with anxious depression.

Drug names: fluoxetine (Prozac and others), gabapentin (Neurontin and others), lamotrigine (Lamictal), tiagabine (Gabitril), topiramate (Topamax).

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REFERENCES

1. Lydiard RB. The role of GABA in anxiety disorders. J Clin Psychiatry 2003;64(suppl 3):21–27
2. Nutt D, Malizia AL. New insights into the role of the GABA(A)-benzodiazepine receptor in psychiatric disorder. Br J Psychiatry 2001;179:390–396
3. Sandford J, Argyropoulos SV, Nutt DJ. The psychobiology of anxiolytic drugs, pt 1: basic neurobiology. Pharmacol Ther 2000;88:197–212
4. Krystal J, Sanacora G, Blumberg H, et al. Glutamate and GABA systems as targets for novel antidepressant and mood-stabilizing treatments. Mol Psychiatry 2002;7(suppl 1):S71–S80
5. Petty F, Kramer GL, Fulton M, et al. Stability of plasma GABA at four-year follow-up in patients with primary unipolar depression. Biol Psychiatry 1995;37:806–810
6. Taylor M, Bhagwagar Z, Cowen PJ, et al. GABA and mood disorders. Psychol Med 2003;33:387–393
7. Emrich HM, von Zerssen D, Kissling W, et al. Effect of sodium valproate on mania: the GABA-hypothesis of affective disorders. Arch Psychiatr Nervenkr 1980;229:1–16
8. Petty F. GABA and mood disorders: a brief review and hypothesis. J Affect Disord 1995;34:275–293
9. Petty F, Kramer GL, Dunnam D, et al. Plasma GABA in mood disorders. Psychopharmacol Bull 1990;26:157–161
10. Petty F, Kramer GL, Gullion CM, et al. Low plasma gamma-aminobutyric acid levels in male patients with depression. Biol Psychiatry 1992;32:354–363
11. Petty F, Schlesser MA. Plasma GABA in affective illness: a preliminary investigation. J Affect Disord 1981;3:339–343
12. Petty F, Sherman AD. Plasma GABA levels in psychiatric illness. J Affect Disord 1984;6:131–138
13. Gerner RH, Hare TA. CSF GABA in normal subjects and patients with depression, schizophrenia, mania, and anorexia nervosa. Am J Psychiatry 1981;138:1098–1101
14. Gold BI, Bowers MB Jr, Roth RH, et al. GABA levels in CSF of patients with psychiatric disorders. Am J Psychiatry 1980;137:362–364
15. Kasa K, Otsuki S, Yamamoto M, et al. Cerebrospinal fluid gamma-aminobutyric acid and homovanillic acid in depressive disorders. Biol Psychiatry 1982;17:877–883
16. Post RM, Ballenger JC, Hare TA, et al. Lack of effect of carbamazepine on gamma-aminobutyric acid in cerebrospinal fluid. Neurology 1980;30: 1008–1011
17. Roy A, Dejong J, Ferraro T. CSF GABA in depressed patients and normal controls. Psychol Med 1991;21:613–618
18. Sanacora G, Gueorguieva R, Epperson CN, et al. Subtype-specific alterations of gamma-aminobutyric acid and glutamate in patients with major depression. Arch Gen Psychiatry 2004;61:705–713
19. Sanacora G, Mason GF, Rothman DL, et al. Reduced cortical gamma-aminobutyric acid levels in depressed patients determined by proton magnetic resonance spectroscopy. Arch Gen Psychiatry 1999;56: 1043–1047
20. Mervaala E, Kononen M, Fohr J, et al. SPECT and neuropsychological performance in severe depression treated with ECT. J Affect Disord 2001;66:47–58
21. Sanacora G, Mason GF, Rothman DL, et al. Increased cortical GABA concentrations in depressed patients receiving ECT. Am J Psychiatry 2003;160:577–579
22. Sanacora G, Mason GF, Rothman DL, et al. Increased occipital cortex GABA concentrations in depressed patients after therapy with selective serotonin reuptake inhibitors. Am J Psychiatry 2002;159:663–665
23. 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
24. Meldrum BS, Chapman AG. Basic mechanisms of gabitril (tiagabine) and future potential developments. Epilepsia 1999;40(suppl 9):S2–S6
25. Suzdak PD, Jansen JA. A review of the preclinical pharmacology of tiagabine: a potent and selective anticonvulsant GABA uptake inhibitor. Epilepsia 1995;36:612–626
26. Bauer J, Bergmann A, Reuber M, et al. Tolerability of tiagabine: a prospective open-label study. Epileptic Disord 2002;4:257–260
27. Crawford P, Meinardi H, Brown S, et al. Tiagabine: efficacy and safety in adjunctive treatment of partial seizures. Epilepsia 2001;42:531–538
28. Dodrill CB, Arnett JL, Shu V, et al. Effects of tiagabine monotherapy on

abilities, adjustment, and mood. Epilepsia 1998;39:33–42
29. Mathias S, Wetter TC, Steiger A, et al. The GABA uptake inhibitor tiagabine promotes slow wave sleep in normal elderly subjects. Neurobiol Aging 2001;22:247–253
30. Berigan T. Treatment of posttraumatic stress disorder with tiagabine [letter]. Can J Psychiatry 2002;47:788
31. Schwartz TL. The use of tiagabine augmentation for treatment-resistant anxiety disorders: a case series. Psychopharmacol Bull 2002;36:53–57
32. Taylor FB. Tiagabine for posttraumatic stress disorder: a case series of 7 women. J Clin Psychiatry 2003;64:1421–1425
33. Zwanzger P, Baghai TC, Schule C, et al. Tiagabine improves panic and agoraphobia in panic disorder patients [letter]. J Clin Psychiatry 2001;62: 656–657
34. 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
35. Crane D. Tiagabine for the treatment of anxiety [letter]. Depress Anxiety 2003;18:51–52
36. Schaller JL, Thomas J, Rawlings D. Low-dose tiagabine effectiveness in anxiety disorders. MedGenMed 2004;6:8
37. Grunze H, Erfurth A, Marcuse A, et al. Tiagabine appears not to be efficacious in the treatment of acute mania. J Clin Psychiatry 1999; 60:759–762
38. Kaufman KR. Adjunctive tiagabine treatment of psychiatric disorders: three cases. Ann Clin Psychiatry 1998;10:181–184
39. Schaffer LC, Schaffer CB. Tiagabine and the treatment of refractory bipolar disorder [letter]. Am J Psychiatry 1999;156:2014–2015
40. Schaffer LC, Schaffer CB, Howe J. An open case series on the utility of tiagabine as an augmentation in refractory bipolar outpatients. J Affect Disord 2002;71:259–263
41. Suppes T, Chisholm KA, Dhavale D, et al. Tiagabine in treatment refractory bipolar disorder: a clinical case series. Bipolar Disord 2002;4: 283–289
42. Nemeroff CB. The role of GABA in the pathophysiology and treatment of anxiety disorders. Psychopharmacol Bull 2003;37:133–146
43. Stahl SM. Anticonvulsants as anxiolytics, pt 1: tiagabine and other anticonvulsants with actions on GABA. J Clin Psychiatry 2004;65:291–292
44. Fava M, Alpert JE, Carmin CN, et al. Clinical correlates and symptom patterns of anxious depression among patients with major depressive disorder in STAR*D. Psychol Med 2004;34:1299–1308
45. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
46. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59(suppl 20):22–33
47. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
48. Williams JB. Standardizing the Hamilton Depression Rating Scale: past, present, and future. Eur Arch Psychiatry Clin Neurosci 2001;251 (suppl 2):II6–II12
49. Bodkin JA, Amsterdam JD. Transdermal selegiline in major depression: a double-blind, placebo-controlled, parallel-group study in outpatients. Am J Psychiatry 2002;159:1869–1875
50. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959;32:50–55
51. Rush AJ, Giles DE, Schlesser MA, et al. The Inventory for Depressive Symptomatology (IDS): preliminary findings. Psychiatry Res 1986;18: 65–87
52. Rush AJ, Gullion CM, Basco MR, et al. The Inventory of Depressive Symptomatology (IDS): psychometric properties. Psychol Med 1996;26: 477–486
53. Endicott J, Nee J, Harrison W, et al. Quality of Life Enjoyment and Satisfaction Questionnaire: a new measure. Psychopharmacol Bull 1993;29: 321–326
54. Guy W. ECDEU Assessment Manual of Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976
55. Buysse DJ, Reynolds CF III, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28:193–213
56. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics 1993;4:353–365
57. Frank E, Prien RF, Jarrett RB, et al. Conceptualization and rationale for consensus definitions of terms in major depressive disorder: remission, recovery, relapse, and recurrence. Arch Gen Psychiatry 1991;48:851–855
58. Sheehan DV. Attaining remission in generalized anxiety disorder: venlafaxine extended release comparative data. J Clin Psychiatry 2001;62 (suppl 19):26–31
59. Walsh BT, Seidman SN, Sysko R, et al. Placebo response in studies of major depression: variable, substantial, and growing. JAMA 2002;287: 1840–1847
60. Adam D, Kasper S, Moller HJ, et al. Placebo-controlled trials in major depression are necessary and ethically justifiable: how to improve the communication between researchers and ethical committees. Eur Arch Psychiatry Clin Neurosci 2005;255:258–260
61. Whyte EM, Dew MA, Gildengers A, et al. Time course of response to antidepressants in late-life major depression: therapeutic implications. Drugs Aging 2004;21:531–554
62. Gabitril [package insert]. West Chester, Pa: Cephalon, Inc; 2005
63. Lydiard RB, Brawman-Mintzer O. Anxious depression. J Clin Psychiatry 1998;59(suppl 18):10–17
64. Altamura AC, Montresor C, Salvadori D, et al. Does comorbid subthreshold anxiety affect clinical presentation and treatment response in depression? a preliminary 12-month naturalistic study. Int J Neuropsychopharmacol 2004;7:481–487
65. Lenze EJ, Mulsant BH, Dew MA, et al. Good treatment outcomes in late-life depression with comorbid anxiety. J Affect Disord 2003;77:247–254
66. Sekula LK, DeSantis J, Gianetti V. Considerations in the management of the patient with comorbid depression and anxiety. J Am Acad Nurse Pract 2003;15:23–33
67. Moller HJ. Anxiety associated with comorbid depression. J Clin Psychiatry 2002;63(suppl 14):22–26
68. Fava M, Evins AE, Dorer DJ, et al. The problem of the placebo response in clinical trials for psychiatric disorders: culprits, possible remedies, and a novel study design approach. Psychother Psychosom 2003;72:115–127