Pattern of Symptom Improvement Following Treatment With Venlafaxine XR in Patients With Generalized Anxiety Disorder

Paolo Meoni, Ph.D.; Eliseo Salinas, M.Sc., M.D.; Yves Brault, M.Sc.; and David Hackett, B.Sc., M.Sc.

Background: The efficacy of anxiolytic drugs in generalized anxiety disorder (GAD) is conventionally assessed by evaluating changes in the total score of psychometric scales such as the Hamilton Rating Scale for Anxiety (HAM-A). The purpose of this pooled analysis of data was to evaluate the efficacy of venlafaxine extended release (XR) on individual items of the HAM-A and the Brief Scale for Anxiety (BSA).

Method: Data were pooled from 5 studies of patients with GAD who were treated with either venlafaxine XR or placebo for 8 weeks (N = 2021) and up to 6 months (N = 767). Individual items of the HAM-A and the BSA were examined, and, using the mean changes from baseline to endpoint, an effect size for each item was calculated by dividing the difference between baseline and endpoint values for each item by the standard deviation of this difference. The effect sizes determined for the venlafaxine group were compared with those for the placebo group. Items from each scale that are concordant with the DSM-IV diagnostic criteria for GAD were selected for further examination, and the specific effect sizes of each item were expressed after controlling for placebo effects.

Results: The effect size of the majority of the 14 items of the HAM-A scale and the 10 items of the BSA scale associated with treatment with venlafaxine XR was greater than with placebo at both 8 weeks and 6 months. Furthermore, the effect sizes at 6 months were generally greater than at 8 weeks in venlafaxine XR–treated patients. Effect sizes associated with venlafaxine XR were greatest for the HAM-A items that were most closely related to diagnostic symptoms of GAD, namely anxious mood, tension, intellectual functioning, and behavior at interview at both 8 weeks and 6 months. Similarly, GAD-related BSA items of inner tension, worrying over trifles, hostile feelings, and muscular tension were associated with the greatest improvements with venlafaxine XR at both timepoints.

Conclusion: The HAM-A and BSA items that most closely corresponded to DSM-IV diagnostic criteria for GAD showed the largest improvement during treatment with venlafaxine XR. This indicates that the specific symptoms of GAD can be treated effectively with venlafaxine XR, both in the short and longer term.

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Received Dec. 19, 2000; accepted June 7, 2001. *From the CNS Department, Wyeth-Ayerst Research, Puteaux, Paris la Defense, Cedex 92301, France.*

Reprint requests to: Paolo Meoni, Ph.D., CNS Department, Wyeth-Ayerst Research, 80 Avenue Du Gen. De Gaulle, 92031 Paris la Defense, Cedex France (e-mail: meonip@war.wyeth.com).

Generalized anxiety disorder (GAD), as defined in the Fourth Edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV),[1] is characterized by the presence of excessive anxiety and worry occurring on more days than not for at least 6 months, in conjunction with at least 3 of a list of 6 symptoms commonly associated with anxiety. These symptoms comprise restlessness, fatigue, concentration difficulties, irritability, muscle tension, and disturbed sleep. The aim of treatment for patients with GAD is to achieve effective control of the core symptoms of the illness, because they can be severely disabling.[2] It is crucial, therefore, that medications used to treat GAD should treat the core symptoms rather than simply masking somatic manifestations of this disorder.

Although the most prominent feature of GAD is chronic worry and its psychic manifestations, patients suffering from GAD are more likely to visit a physician because of somatic symptoms related to anxiety,[3] and the control of such symptoms may therefore become the principal focus of treatment. Different treatments have been reported to show varying profiles of response for different symptoms of anxiety. Notably, benzodiazepines have been reported to be more specific for somatic symptoms and antidepressants, for psychic symptoms of anxiety.[4,5] In a study comparing imipramine, trazodone, and diazepam in patients with GAD,[4] imipramine had a significantly greater effect than diazepam on the psychic factor score of the Hamilton Rating Scale for Anxiety (HAM-A) at week 8, while diazepam had a significantly greater effect than both antidepressants on the HAM-A somatic factor score during the first 2 weeks of therapy. Other studies have also suggested differential effects for diazepam and buspirone in patients with anxiety disorders.[6–10] For example, whereas diazepam reduced the HAM-A somatic factor score by 65% after 6 weeks of treatment in women with GAD, the psychic factor score was reduced by only 52%.[10]

Measurement of changes in the severity of anxiety symptoms during treatment is conventionally performed using established assessment instruments. The HAM-A, for example, comprises 14 separate items that are related to the 2 clusters of symptoms of anxiety, psychic and somatic.[11] The psychic cluster of symptoms comprises anxious mood, tension, fears, insomnia, intellectual (cognitive) changes, depressed mood, and behavior at interview. The somatic symptom cluster comprises somatic muscular, somatic sensory, cardiovascular, respiratory, gastrointestinal, genitourinary, and autonomic symptoms. Each item in these symptom clusters is rated on a 5-point scale from 0 (none) to 4 (very severe). Another instrument for measuring symptom severity in anxiety disorders is the Brief Scale for Anxiety (BSA),[12] which includes 10 separate items, each rated on a 7-point scale from 0 (none) to 6 (severe). Investigation of the effect of treatment on specific symptoms of GAD using these assessment instruments is, however, constrained by the fact that they have not been validated specifically for use in patients with GAD as it is currently defined. Furthermore, the total scores from the HAM-A and BSA rating instruments allocate approximately equal weights to somatic and psychic components of anxiety, which means that these instruments may not be wholly appropriate for evaluating the characteristic symptomatology of GAD.

While a number of the symptoms included in items from each of these assessment instruments are characteristic and diagnostic for GAD, results from studies usually report data that are derived from total scores, rather than from information about the effect of treatment on the individual component items of these scales. This gives a less detailed picture than an analysis of the effect of treatment on items that comprise clusters of individual symptoms. An analysis of individual component items specific to GAD may, on the other hand, provide important information about the efficacy profile of drugs in the treatment of GAD over and above that obtained from traditional analyses.

Information about the degree of effect of a drug on different items of a scale that have different baseline values can be obtained using "effect size" as a descriptive rather than inferential measure of change.[13] This approach, which allows a direct evaluation of the magnitude of the effect of a treatment relative to the variation during the natural course of an illness, has been used to analyze data from studies with the extended-release formulation of the specific serotonin and norepinephrine reuptake inhibitor venlafaxine (venlafaxine XR) in patients with GAD.

In controlled clinical trials, venlafaxine has been shown to be an effective and well-tolerated agent for the treatment of major depression,[14,15] anxiety associated with depression,[16] comorbid depression and anxiety,[17] and GAD.[18–22] In the present analysis of pooled data from 5 clinical studies of the efficacy of venlafaxine XR in the treatment of GAD,[18–22] changes in those individual symptom or item scores from HAM-A and BSA scales that are concordant with the defined symptoms of GAD were evaluated in parallel. This approach made it possible to examine the effect size of venlafaxine XR on the core features of GAD as well as on other specific symptoms that characterize the disorder using 2 distinct scales.

METHOD

Design of Studies

Each of the 5 studies[18–22] included in this pooled analysis involved nondepressed patients who exhibited DSM-IV diagnostic criteria for GAD, which comprise the core symptoms of this condition. Each study had a placebo-controlled, double-blind treatment phase preceded by a 4- to 10-day washout period before patients were randomly assigned to study treatment. Three studies were of 8 weeks' treatment duration, and 2 studies were of 6 months' duration.

Study 1[18] was an 8-week dose-finding study of venlafaxine XR (75, 150, and 225 mg once daily) in 349 patients. Study 2[19] was an 8-week comparison of venlafaxine XR (75 and 150 mg once daily) and buspirone (30 mg/day) in 365 patients. Study 3[20] was a flexible-dose study of venlafaxine XR (75–225 mg/day) for up to 6 months in 238 patients. Study 4[21] compared 2 fixed doses of venlafaxine XR (75 mg/day and 150 mg/day) with diazepam (15 mg/day) during short-term (8 weeks) administration in 540 patients. Study 5[22] compared the effects of 3 fixed doses of venlafaxine XR (37.5, 75, and 150 mg once daily) in 529 patients for up to 6 months. All studies included the HAM-A as the principal assessment instrument, and, additionally, 2 studies[21,22] included the BSA scale.

In all studies, eligible patients were at least 18 years old and met DSM-IV criteria for GAD. The total baseline score on the HAM-A was at least 18 (Studies 1, 2, and 3) or 20 (Studies 4 and 5), together with baseline scores for items 1 (anxious mood) and 2 (tension) of at least 2. Patients were required to have a total score on the Covi Anxiety Scale[23] that was greater than the total score on the Raskin Depression Scale,[24] where the latter score was not greater than 9. In the original trials, these assessments were secondary measures to ensure the exclusion of patients with major depressive disorder (DSM-IV) currently or in the previous 6 months or with a mainly depressive symptomatology.

An intent-to-treat population formed the basis of this pooled analysis. This population is defined as all patients with a baseline value for the primary efficacy measure who (a) took at least 1 dose of study medication and (b) had at least 1 primary efficacy evaluation, either during therapy, or within 3 days of the last time that study medication had been taken.

Table 1. Absolute Effect Size of Venlafaxine Extended Release (XR) on Hamilton Rating Scale for Anxiety (HAM-A) Items in the Short and Longer Term Compared With Placebo

HAM-A Item[a] (item number)	Placebo		Venlafaxine XR	
	Week 8	Month 6	Week 8	Month 6
(1) Anxious mood	1.0	0.9	1.4	1.5
(2) Tension	0.9	0.9	1.3	1.4
(3) Fears	0.7	0.5	0.8	0.8
(4) Insomnia	0.6	0.6	0.8	1.0
(5) Intellectual	0.7	0.7	1.0	1.1
(6) Depressed mood	0.3	0.3	0.7	0.7
(7) Somatic muscular	0.7	0.8	0.9	1.0
(8) Somatic sensory	0.6	0.6	0.7	0.8
(9) Cardiovascular	0.6	0.6	0.8	0.9
(10) Respiratory	0.7	0.7	0.9	0.9
(11) Gastrointestinal	0.7	0.7	0.7	0.8
(12) Genitourinary	0.6	0.7	0.5	0.6
(13) Autonomic	0.7	0.6	0.7	0.8
(14) Behavior at interview	0.8	0.8	1.1	1.2

[a]Items 1 to 6 and 14 relate to psychic symptoms of anxiety. Items 7 to 13 relate to somatic symptoms.[11]

Table 2. Absolute Effect Size of Venlafaxine Extended Release (XR) on Brief Scale for Anxiety (BSA) Items in the Short and Longer Term Compared With Placebo

BSA Item[12] (item number)	Placebo		Venlafaxine XR	
	Week 8	Month 6	Week 8	Month 6
(1) Inner tension	0.8	0.8	1.2	1.3
(2) Hostile feelings	0.7	0.7	0.9	1.0
(3) Hypochondriasis	0.5	0.5	0.7	0.7
(4) Worrying over trifles	0.8	0.9	1.1	1.3
(5) Phobias	0.7	0.6	0.7	0.8
(6) Reduced sleep	0.5	0.5	0.7	0.8
(7) Autonomic I[a]	0.7	0.7	0.9	1.0
(8) Aches and pains	0.5	0.4	0.7	0.8
(9) Autonomic II[a]	0.7	0.6	0.9	0.9
(10) Muscular tension	0.7	0.7	1.0	1.1

[a]Autonomic I is scored for described symptoms. Autonomic II is scored for observed signs.

Statistical Analysis

The primary efficacy parameter used in this analysis was, for all studies, the change in the total HAM-A score between baseline and the end of therapy. Studies 4 and 5 also included BSA evaluations at baseline and during the course of the studies. Data were pooled from all studies, and mean changes in HAM-A and BSA item scores in the venlafaxine XR and placebo treatment groups were determined. The magnitude of the improvement in mean item score for each item (the effect size) was calculated as the difference in the mean score between baseline (pretreatment) and the end of 8 weeks (all 5 studies) and 24 weeks (Studies 3 and 5) of therapy, divided by the standard deviation of that difference. An effect size of 0.8 is considered to be large.[4] The present results focus on individual HAM-A and BSA item effect sizes after 8 weeks and after 6 months of treatment.

The specific treatment effect of venlafaxine XR (differential effect size) was calculated as the difference between the effect size observed in the active treatment group and that in the placebo group. In this way, data on the specific benefit attributable to venlafaxine XR treatment were evaluated for each rating scale item.

RESULTS

Treatment with venlafaxine XR in patients with GAD was clearly associated with a reduction in severity of all anxiety symptoms (Table 1). After 8 weeks' treatment, the effect size in 11 of the 14 HAM-A items was greater with venlafaxine XR than with placebo. In particular, venlafaxine XR was associated with the greatest effect size for anxious mood (item 1), tension (item 2), intellectual (item 5), and behavior at interview (item 14). After 6 months' treatment, the effect size in the venlafaxine XR–treated patients had increased compared with the 8-week value for 11 of the 14 HAM-A items. Furthermore, the effect sizes in the venlafaxine XR–treated patients for anxious mood (item 1), tension (item 2), insomnia (item 4), intellectual functioning (item 5), somatic sensory (item 8), cardiovascular (item 9), gastrointestinal (item 11), autonomic (item 13), and behavior at interview (item 14) had all increased in magnitude relative to placebo.

A similar pattern of results was seen in the BSA item scores (Table 2). At 8 weeks, the greatest effect size in the venlafaxine XR–treated patients was seen for inner tension (item 1), worrying over trifles (item 4), and muscular tension (item 10). By 6 months, not only had the effect size of these items increased, the effect sizes of hostile feelings (item 2), phobias (item 5), reduced sleep (item 6), autonomic I (item 7), and aches and pains (item 8) had all increased relative to placebo (Table 2).

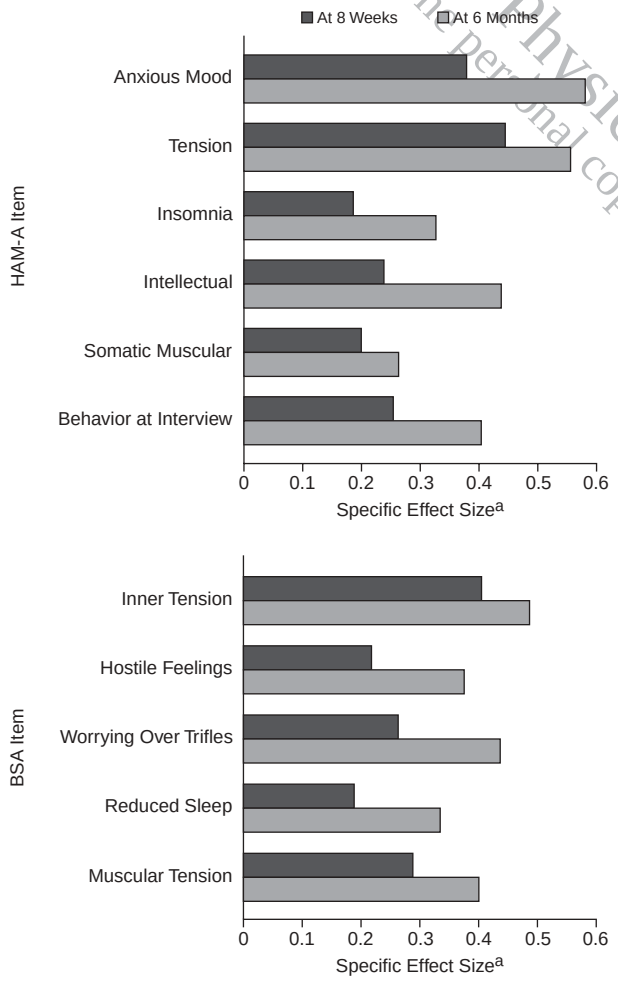
Items from each of these 2 rating instruments that included symptoms associated with the DSM-IV diagnostic criteria for GAD are, from the HAM-A scale, anxious mood, tension, insomnia, intellectual, somatic muscular, and behavior at interview and, from the BSA scale, inner tension, hostile feelings, worrying over trifles, reduced sleep, and muscular tension (Table 3). When specific effect sizes, expressed in terms of the difference between the absolute effect sizes with venlafaxine XR and placebo, are considered, all of these GAD-concordant symptoms showed a specific effect size that is greater than placebo both in the short term (8 weeks) and in the longer term (6 months). Further, the specific effect sizes for all GAD-concordant items were greater in the longer term than in the short term (Figure 1).

Treatment with venlafaxine XR was associated with the greatest specific effect size for GAD-concordant symptoms on the HAM-A scale of anxious mood and tension at both time intervals (Figure 1). Similarly, the specific effect sizes associated with venlafaxine XR were greatest for GAD-related items of inner tension, worrying over trifles, and muscular tension on the BSA scale at both time intervals (Figure 1).

Table 3. Symptom Concordance Between Generalized Anxiety Disorder (GAD) and the Hamilton Rating Scale for Anxiety (HAM-A) and Brief Scale for Anxiety (BSA)

DSM-IV Criterion for GAD[1]	Corresponding HAM-A Item[11]	Corresponding BSA Item[12]
Excessive anxiety and worry occurring more days than not for at least 6 months	Anxious mood	Inner tension; worrying over trifles
Restlessness	Tension; behavior at interview	Inner tension
Easily fatigued	Tension	…
Difficulty concentrating	Intellectual	…
Irritability	Anxious mood	Hostile feelings
Muscle tension	Somatic muscular; behavior at interview	Muscular tension
Disturbed sleep	Insomnia	Reduced sleep

Figure 1. Specific Effect Size Relative to Placebo on Hamilton Rating Scale for Anxiety (HAM-A) and Brief Scale for Anxiety (BSA) Items That Are Concordant With DSM-IV Generalized Anxiety Disorder (GAD) Symptoms in Patients Treated With Venlafaxine Extended Release (XR) in the Short and Longer Term



[a]Absolute effect size for venlafaxine XR minus absolute effect size for placebo.

DISCUSSION

The current description of GAD in the DSM-IV is the culmination of over 2 decades of research in anxiety disorders. This evolution has enabled GAD to be distinguished from mood disorders, other anxiety disorders, and from anxiety symptoms that are considered to be a normal part of everyday life. Symptoms associated with GAD that can be used for diagnostic purposes have evolved from DSM-III to DSM-IV criteria to reflect the concept of a predominantly psychic condition. However, as many of the instruments used to evaluate symptom severity in anxiety disorders predate the current definition of GAD, some discrepancies between the GAD symptomatology as described in DSM-IV and those symptoms included in psychometric rating scales commonly used in clinical studies, such as the HAM-A and BSA, are inevitable.

Nevertheless, most of the diagnostic symptoms of GAD are contained in either or both the HAM-A and BSA rating scales (Table 3), albeit along with other symptoms of anxiety that cannot be considered specific for GAD. In particular, somatic symptoms of anxiety measured by the HAM-A scale, such as cardiovascular, respiratory, gastrointestinal, and genitourinary items, are much more comprehensive than those required for a diagnosis of GAD and may represent those symptoms that are most easily perceived by patients. Effective treatment of these somatic symptoms in GAD patients is therefore desirable. Such improvement in somatic symptoms is likely to follow and augment the alleviation of the core of GAD-specific symptoms.

The 2 scales considered in this study do differ in their ability to measure GAD severity. While the HAM-A rating scale includes all GAD-specific symptoms (together with other nonspecific symptoms of anxiety), the BSA scale does not. The BSA scale, for example, does not include GAD-specific symptoms of being easily fatigued and difficulty concentrating, both of which are diagnostic for GAD (Table 3). However, the BSA scale is more explicit in scoring for the key diagnostic symptom of GAD of uncontrollable worry. Results from the HAM-A were, however, of primary interest.

The present analysis of individual items on the HAM-A and BSA rating scales showed that an effect size of 0.8, which is considered to be large,[4] occurred much more frequently in GAD patients treated with venlafaxine XR than in patients treated with placebo. In the few items where the effect size with placebo was ≥ 0.8, the corresponding effect size for venlafaxine XR was always greater. A further finding from this investigation was that the effect size for individual items was either maintained or increased during long-term treatment, indicating that additional benefit can be obtained in GAD patients from continued treatment with venlafaxine XR.

The specificity of venlafaxine XR on anxiety symptoms makes it unlikely for this effect to be due to the antidepressant activity of this drug. Any contribution of antidepressant activity to the efficacy in the treatment of GAD was precluded in these trials by strict exclusion criteria; patients were required to have an absence of a diagnosis of major depressive disorder and, at worst, could have low-grade depressive symptoms. Furthermore, the exclusion of depressed patients or patients with mainly depressive symptomatology from the studies in this analysis is reflected by the fact that venlafaxine XR had a relatively modest absolute effect on the depressed mood item of HAM-A (Table 1). Nevertheless, in spite of the "non-depressed" selection criterion in this population, the specific effect (i.e., controlling for placebo effect) on depressed mood that was a component of an anxiety state was much stronger, underlining the efficacy of venlafaxine XR on this depressive symptom.

In the light of the present findings, clusters of symptoms contained in different HAM-A and BSA items cannot be considered to be unequivocally homogeneous in their clinical relevance to GAD nor in their capability to measure response of GAD symptoms to treatment. Nevertheless, using the symptom concordance principle, the improvement seen in GAD patients following active treatment with venlafaxine XR is mainly observed in the core of GAD-specific symptoms that are consistent with DSM-IV diagnostic criteria for this condition. Furthermore, changes in the individual item scores are likely to represent a more indicative measure of a patient's recovery and well-being than the total score. This positive effect of venlafaxine XR on individual items is independent of placebo effects in this group of patients as indicated by the magnitude of the specific effect size on these symptoms.

The traditional use of psychiatric rating scales in clinical trials of pharmacotherapy has been to compare the mean score at baseline with the mean score during and after treatment. The difference in scores is then related to the global effect of treatment. Although this approach is justified with rating scales that are purely unidimensional, concerns have been raised about the homogeneity of the HAM-A.[25] A more informative approach may be to use all the information contained in individual items to evaluate symptom-specific effects of treatment. The heterogeneity of measurement instruments supports the individual item analysis approach for multidimensional disorders such as GAD. For example, individual item analysis has been used to examine the efficacy of buspirone compared with placebo in GAD using data pooled from 6 studies in which the HAM-A was the principal assessment instrument.[26] Relative improvement in individual items was found to be heterogeneous, and percent improvements on baseline values ranged from 48.9% (behavior at interview) to 31.7% (genitourinary symptoms). Effect size, derived from pooled HAM-A data, has also been used to detect differential effects of alprazolam, imipramine, and placebo on different aspects of depression, revealing distinct symptom-specific effects of different medications.[13] The results of the present analyses support the usefulness of this methodological approach.

The specific improvement in the cluster of diagnostic symptoms for GAD including anxious mood, tension, insomnia, intellectual functioning, somatic muscular symptoms, and behavior at interview might, therefore, represent the best indicators of patients' responses to GAD treatment. Results from the present analysis show for the first time that in patients with GAD, a specific improvement is observed in the core symptoms of this disorder following venlafaxine XR therapy. This indicates that the impact of GAD in patients suffering from this potentially disabling condition can be ameliorated in the short term by treatment with venlafaxine XR and that this reduced symptomatology can be enhanced in the longer term by continuous treatment with this medication.

Drug names: alprazolam (Xanax and others), diazepam (Valium and others), trazodone (Desyrel and others), venlafaxine (Effexor).

REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
2. Wittchen HU, Zhao S, Kessler RC, et al. DSM-III-R generalized anxiety disorder in the National Comorbidity Survey. Arch Gen Psychiatry 1994; 51:355–364
3. Maier W, Gansicke M, Freyberger HJ, et al. Generalized anxiety disorder (ICD-10) in primary care from a cross-cultural perspective: a valid diagnostic entity? Acta Psychiatr Scand 2000;101:29–36
4. Rickels K, Downing R, Schweizer E, et al. Antidepressants for the treatment of generalized anxiety disorder: a placebo-controlled comparison of imipramine, trazodone, and diazepam. Arch Gen Psychiatry 1993;50: 884–895
5. Rickels K, Schweizer E. The clinical presentation of generalized anxiety in primary care settings: practical concepts of classification and management. J Clin Psychiatry 1997;58(11, suppl):4–10
6. van Laar MW, Volkerts ER, van Willigenburg AP. Therapeutic effects and effects on actual driving performance of chronically administered buspirone and diazepam in anxious outpatients. J Clin Psychopharmacol 1992; 12:86–95
7. Fontaine R, Annable L, Chouinard G, et al. Bromazepam and diazepam in generalized anxiety: a placebo-controlled study with measurement of drug plasma concentrations. J Clin Psychopharmacol 1983;3:80–87
8. Rickels K, Wiseman K, Norstad N, et al. Buspirone and diazepam in anxiety: a controlled study. J Clin Psychiatry 1982;43(12, sec 2):81–86
9. Pecknold JC, Matas M, Howarth BG, et al. Evaluation of buspirone as an antianxiety agent: buspirone and diazepam versus placebo. Can J Psychiatry 1989;34:766–771
10. Pourmotabbed T, McLeod DR, Hoehn-Saric R, et al. Treatment, discontinuation, and psychomotor effects of diazepam in women with generalized anxiety disorder. J Clin Psychopharmacol 1996;16:202–207
11. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959;32:50–55
12. Tyrer P, Owen RT, Cicchetti DV. The brief scale for anxiety: a subdivision of the comprehensive psychopathological rating scale. J Neurol Neurosurg Psychiatry 1984;47:970–975
13. Leon AC, Shear MK, Portera L, et al. Effect size as a measure of symptom-specific drug change in clinical trials. Psychopharmacol Bull 1993;29: 163–167

14. Einarson TR, Arikian SR, Casciano J, et al. Comparison of extended-release venlafaxine, selective serotonin reuptake inhibitors, and tricyclic antidepressants in the treatment of depression: a meta-analysis of randomized controlled trials. Clin Ther 1999;21:296–308
15. Entsuah AR, Rudolph RL, Chitra R. Effectiveness of venlafaxine treatment in a broad spectrum of depressed patients: a meta-analysis. Psychopharmacol Bull 1995;31:759–766
16. Rudolph RL, Entsuah R, Chitra R. A meta-analysis of the effects of venlafaxine on anxiety associated with depression. J Clin Psychopharmacol 1998;18:136–144
17. Silverstone PH, Ravindran A, for the Venlafaxine XR 360 Study Group. Once-daily venlafaxine extended release (XR) compared with fluoxetine in outpatients with depression and anxiety. J Clin Psychiatry 1999;60: 22–28
18. Rickels K, Pollack MH, Sheehan DV, et al. Efficacy of extended-release venlafaxine in nondepressed outpatients with generalized anxiety disorder. Am J Psychiatry 2000;157:968–974
19. Davidson JRT, DuPont RL, Hedges D, et al. Efficacy, safety, and tolerability of venlafaxine extended release and buspirone in outpatients with generalized anxiety disorder. J Clin Psychiatry 1999;60:528–535
20. Gelenberg AJ, Lydiard RB, Rudolph RL, et al. Efficacy of venlafaxine extended-release capsules in nondepressed outpatients with generalized anxiety disorder: a 6-month randomised controlled trial. JAMA 2000;283: 3082–3088
21. Hackett D, Haudiquet V, Salinas E. Controlling for the placebo response rate: a methodological approach to data from double-blind studies with high placebo reponse. J Clin Psychopharmacol 1999;13(3, suppl A). Abstract P138:A44
22. Hackett D, Haudiquet V, Salinas E. A dose-response, 6 month evaluation of venlafaxine extended-release in outpatients with generalized anxiety disorder. J Clin Psychopharmacol 1999;13(3,suppl A). Abstract P139:A44
23. Lipman R, Covi L. Outpatient treatment of neurotic depression: medication and group psychotherapy. In: Spitzer RL, Klein DL, eds. Evaluation of the Psychological Therapies. Baltimore, Md: Johns Hopkins University Press; 1976
24. Raskin A, Schulterbrandt JG, Reatig N. Rater and patient characteristics associated with rater differences in psychiatric scale ratings. J Clin Psychol 1966;22:417–423
25. Gjerris A, Bech P, Bøjholm B, et al. The Hamilton Anxiety Scale: evaluation of homogeneity and inter-observer reliability in patients with depressive disorders. J Affect Disord 1983;5:163–170
26. Feighner, JP, Cohn JB. Analysis of individual symptoms in generalized anxiety: a pooled, multistudy, double-blind evaluation of buspirone. Neuropsychobiology 1989;21:124–130