Venlafaxine Extended Release (XR) in the Treatment of Generalized Anxiety Disorder

David V. Sheehan, M.D., M.B.A.

This article reviews results of reports suggesting that venlafaxine extended release (XR) may play an important role in the treatment of anxiety disorders, particularly generalized anxiety disorder (GAD). Statistically significant improvements in GAD for venlafaxine XR compared with placebo on the basis of the Hamilton Rating Scale for Anxiety were seen in the acute treatment studies up to 8 weeks and were maintained for 6 months. One comparative study found venlafaxine XR to be as effective as, or on some measures more effective than, buspirone at relieving GAD. Venlafaxine XR was safe and well tolerated in the GAD studies, with discontinuation rates due to adverse effects similar to the rates seen with placebo or buspirone. *(J Clin Psychiatry 1999;60[suppl 22]:23–28)*

Generalized anxiety disorder (GAD) is a multidimensional psychiatric disorder that is more commonly associated with depression than are other anxiety disorders. Because of the strong association between GAD and depression and the clinical consequences of this comorbidity in poorer prognosis, antidepressants are often used to treat GAD. Whereas traditional treatments for anxiety such as the benzodiazepines and the anxiolytic buspirone have shown little efficacy in the treatment of depression, antidepressants have a long history of use in the treatment of anxiety disorders. Furthermore, using one agent to treat both conditions may have important implications in improving outcomes and making GAD easier to treat.

Improving the treatment of GAD is important in primary care settings, where it is seen frequently. In one study reported by Lecrubier and Hergueta,[1] general practitioners underrecognized both depression and anxiety compared with those who used a "gold standard" structured interview to diagnose patients with depression or anxiety. As a consequence, depressed patients misdiagnosed with an anxiety disorder were treated with anxiolytics much more often than with antidepressants. In fact, only 13% of all depressed patients received antidepressant treatment. Treatment choices were not necessarily improved when the underlying psychiatric disorder was accurately identified. In the 11.4% of patients with an "anxiodepressive syndrome" identified by general practitioners, the majority of patients were treated with anxiolytics.[1] Thus, given the considerable overlap between GAD and depression and the cost of mistaking depression for an anxiety disorder, there is value in having a single agent that is effective for both disorders. Using a single agent has the additional public health benefit of offsetting diagnostic error by the clinician who mistakenly identifies a case of depression as GAD by effectively treating either or both disorders with the same medication.

Not surprisingly, misdiagnosis and inadequate treatment of GAD have a substantially negative impact on health care costs. Among primary care patients, those identified as distressed high utilizers of medical care (i.e., those having a high prevalence of chronic medical problems and significant limitation of activities as a result of their illness) most commonly have either major depression or GAD. Of 119 distressed high utilizers, 21.8% had a diagnosis of GAD, which was a higher rate than for panic disorder (16.8%), somatization disorder (20.2%), dysthymic disorder (16.8%), or alcohol abuse (5.0%), and only a lower rate than that for major depression (23.5%).[2] The somatic symptoms associated with GAD probably contribute to the challenges of proper diagnosis and highlight the need for therapies that improve both the psychic and somatic manifestations of this disorder.

There are unmet needs in the diagnosis and treatment of GAD among primary care patients. As noted, although agents such as the benzodiazepines and buspirone may alleviate anxiety, these agents have little effect on the depression that commonly co-occurs with this disorder. Treatment with antidepressants has opened up a new arena of investigation in GAD, with a growing body of evidence supporting the role of newer therapies, such as venlafaxine extended release (XR), an antidepressant with mixed

From the University of South Florida, Institute for Research in Psychiatry, Tampa.

Presented at the Depression/Anxiety Working Group Conference, a scientific experts' meeting, held January 30–31, 1999, in Dallas, Tex. This conference was supported by an unrestricted educational grant from Wyeth-Ayerst Laboratories.

Reprint requests to: David V. Sheehan, M.D., M.B.A., 3515 E. Fletcher Ave., Tampa, FL 33613.

serotonin-norepinephrine reuptake inhibition. In contrast to the older tricyclic antidepressants, venlafaxine XR has a generally more favorable adverse effect profile and greater patient tolerability. The following discussion reviews the background on the use of venlafaxine in anxiety disorders and recent randomized, placebo-controlled clinical trials that highlight efficacy and safety data that led to the recent U.S. Food and Drug Administration approval of venlafaxine XR for treating GAD.

RATIONALE FOR THE TREATMENT OF ANXIETY WITH VENLAFAXINE

Preliminary Data in GAD, Panic Disorder, Social Phobia, and Obsessive-Compulsive Disorder

Several studies and case series suggest that venlafaxine is effective in anxiety disorders including GAD,[3] panic disorder,[4–6] social phobia,[7] and obsessive-compulsive disorder (OCD).[8–12] In addition to these reports, Ninan and colleagues[13] evaluated venlafaxine in a phase I trial in the treatment of trichotillomania, which is closely related to OCD. These data on venlafaxine in anxiety disorders provided the impetus to comprehensively evaluate the efficacy of venlafaxine XR in the treatment of GAD.

Johnson et al.[3] reported results of an open, prospective evaluation of venlafaxine in 11 patients whose symptoms met DSM-III-R criteria for GAD. Patients were treated for 1 to 36 weeks with modest doses of venlafaxine (12.5–187.5 mg/day). Marked or moderate improvement in symptoms, as defined by a Clinical Global Impressions (CGI) scale score of 1 or 2 and a score < 10 on the Hamilton Rating Scale for Anxiety (HAM-A), was seen in 8 (73%) of 11 patients. The authors noted that venlafaxine produced reductions in anxiety scores that "were typically profound" with symptoms remitting completely in several patients. In 3 patients, the positive results of treatment were maintained over 8 months of therapy.

Two preliminary studies suggest that venlafaxine may also be effective in panic disorder.[5,6] In the first, an open-label, prospective study,[5] 13 patients were followed for 10 weeks and received doses ranging from 6 mg/day to 225 mg/day by the end of the study. A significant improvement was found in mean ± SD HAM-A scores from 15.3 ± 3.6 at baseline to 3.2 ± 1.6 at week 10 ($p < .0001$). Six patients responded to doses of 75 mg/day or lower.[5] In the second study,[6] 25 patients with panic disorder enrolled in a 5-center, double-blind, placebo-controlled trial. Statistically significant changes on CGI-Global Improvement item scores were observed with venlafaxine versus placebo at endpoint with an effect size of 0.89. Improvements in the Marks-Sheehan phobia rating (fear) score and in HAM-A and Hamilton Rating Scale for Depression (HAM-D) scores at endpoint with venlafaxine treatment compared with placebo were also observed. In general, the overall magnitude of response with venlafaxine at endpoint (0.39)[6] was comparable to responses previously reported for other antidepressants (0.55) and benzodiazepines (0.40), indicating that the improvement with venlafaxine is comparable to that seen with other therapies.[14]

Venlafaxine has also been evaluated in patients with social phobia. Kelsey[7] reported the results of a retrospective chart analysis of 9 patients treated with a mean final dose of venlafaxine of 146.5 mg/day for 4 to 12 weeks. Eight of the 9 patients had previously failed therapy with a selective serotonin reuptake inhibitor (SSRI) or could not tolerate SSRI-related adverse effects. Venlafaxine treatment was associated with significant improvement in the social phobia subscale of the Fear Questionnaire ($p < .02$) and in the social/leisure subscales of the Sheehan Disability Scale ($p < .02$). Overall, venlafaxine was effective in the treatment of social phobia in 8 of 9 patients.[7]

Several studies have examined the use of venlafaxine in the treatment of patients meeting the diagnostic criteria for OCD.[7–10,12] Rauch and colleagues[12] used venlafaxine in a series of 10 patients whose symptoms met DSM-IV criteria for OCD. Consistent with findings from studies of SSRIs in OCD, 3 (30%) of 10 patients were responders to venlafaxine at doses of 150 to 375 mg/day (mean dose = 308.3 mg/day) based on a ≥ 35% reduction in Yale-Brown Obsessive Compulsive Scale scores. Four (40%) of 10 patients were considered responders (defined by CGI scores of 1 or 2, i.e., marked or moderate improvement). The modest efficacy of venlafaxine reported in this case series (an effect size of 1.27) is similar to that reported in a meta-analysis of several SSRIs used in OCD.[15] These improvements in the symptoms of OCD were apparent even in the absence of a treatment effect on the Beck Depression Inventory (and, therefore, appear to be independent of venlafaxine's antidepressant effects) and were more robust in treatment-naive patients.[12] These results are supported by an open-label retrospective review[8] of 2 OCD patients who showed marked improvement during treatment with venlafaxine, 150 mg/day, after previously failing therapy or discontinuing because of adverse side effects with an SSRI.

Finally, in a small, phase I, open-label trial of 12 patients with trichotillomania,[13] venlafaxine doses of 150 to 375 mg/day produced a response in 8 (67%) of 12 patients. As with other reports, the authors of this study hypothesized that venlafaxine's dual inhibition of serotonin and norepinephrine reuptake provided substantial treatment benefits in patients with obsessive-compulsive symptomatology.

Results of Studies in Patients With Major Depression and Comorbid Anxiety

The early reports of venlafaxine's efficacy in a range of anxiety disorders generated interest in the possibility that its anxiolytic benefits were independent of its antidepressant effects. To investigate this hypothesis further, prospective controlled trials were conducted in patients with

comorbid anxiety and major depression, and databases on depressed patients with and without comorbid anxiety were retrospectively analyzed to examine venlafaxine's antianxiety effects more closely. Data were collected on both venlafaxine[3,16] and venlafaxine XR.[17,18] In the meta-analysis of 6 studies (3 placebo-controlled fixed-dose studies and 3 placebo- and comparator-controlled flexible-dose studies) by Rudolph et al.,[19] 1398 (86%) of 1627 patients included in the intent-to-treat analyses were categorized as anxious, depressed patients (with anxiety defined by a baseline score ≥ 2 on the HAM-D psychic anxiety item). These anxious, depressed patients had a statistically significantly higher response rate with venlafaxine than with placebo beginning at week 1 of treatment.[19] Similar prospective studies of patients with major depression associated with anxiety who were treated with venlafaxine showed that these improvements are dose related.[16]

Studies of venlafaxine XR are consistent with the findings of venlafaxine in anxious, depressed patients. In the report by Feighner and colleagues,[17] venlafaxine XR was statistically superior to placebo in reducing the HAM-D psychic anxiety item score after 1 week of treatment in depressed patients with moderate or severe anxiety. Although not statistically significant, the reduction in scores was greater for venlafaxine XR than for venlafaxine from week 3 onward.[17] In a flexible-dose trial comparing venlafaxine XR and fluoxetine in outpatients with major depression and coexisting anxiety in which anxiolytic effect was measured using the HAM-A, the response rate at week 12 was significantly higher in the venlafaxine XR group than in the fluoxetine group.[18]

CONTROLLED TRIALS OF VENLAFAXINE XR IN GAD

Taken together, these findings have important implications for the treatment of GAD with venlafaxine XR. Patients with GAD have high rates of comorbid depression, and the association of anxiety and depression complicates treatment, leads to a more chronic course of illness, and more often results in poor outcomes compared with either anxiety or depression alone.[20,21] Therefore, effective treatment of GAD may require an agent with both potent antidepressant and anxiolytic actions. Previous studies in patients whose symptoms met DSM-III criteria for GAD and who had HAM-A scores > 18 at baseline have shown that the tricyclic imipramine is an effective agent, although patients reported a higher rate of adverse events compared with patients treated with a benzodiazepine.[22] The limitations of benzodiazepine therapy, however, and the lack of significant antidepressant effects with buspirone, support the development of an agent that provides the efficacy of tricyclic antidepressants with greater tolerability.

Venlafaxine XR is a potent antidepressant that lacks the anticholinergic side effects of the tricyclics, and the preliminary data reviewed above indicate the potential for efficacy in treating anxiety. Therefore, rigorously designed studies of strictly defined GAD patient populations were undertaken to assess the safety and efficacy of venlafaxine XR in GAD. Three of these placebo-controlled studies[23–25] are reviewed in detail here, including 2 short-term (8-week) studies, one using fixed doses of venlafaxine XR between 75 and 225 mg/day[23] and the other using fixed doses between 75 and 150 mg/day.[24] The latter study also compared venlafaxine XR with buspirone, 30 mg/day. In the third study, flexible doses of venlafaxine XR (75–225 mg/day) were compared with placebo for 28 weeks.[25] Finally, preliminary results of a 6-month, randomized, fixed-dose study of venlafaxine XR are also presented.[26]

Table 1. Primary Inclusion and Exclusion Criteria for All Studies of Venlafaxine XR in GAD[a]

Inclusion Criteria
DSM-IV criteria for GAD
Baseline HAM-A score ≥ 18[23–25] or ≥ 20[26]
HAM-A items 1 (anxious mood) and 2 (tension) ≥ 2
Raskin score ≤ 9
Covi Anxiety Scale score > Raskin score
Exclusion Criteria
Recent history of major depressive disorder (at screening or within 6 months of study)
Raskin score > 3 on any single item

[a]Data from references 23–26. Abbreviations: GAD = generalized anxiety disorder, HAM-A = Hamilton Rating Scale for Anxiety, Raskin = Raskin Depression Rating Scale, XR = extended release.

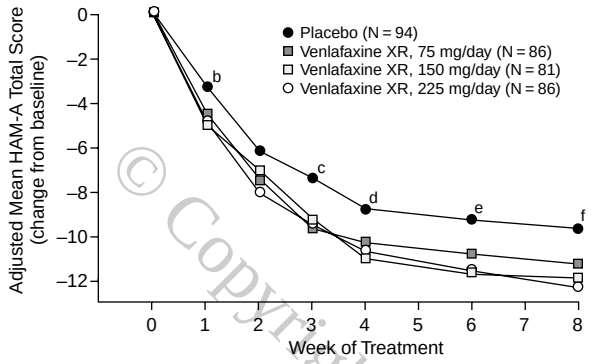
The venlafaxine XR treatment studies used the DSM-IV criteria for GAD in patient selection. Table 1 shows the primary inclusion and exclusion criteria used in these studies. To evaluate patients with "pure" GAD, patients with a recent history of major depressive disorder were excluded, as were those with a Raskin Depression Rating Scale score above 3 on any single item on the scale.[23–26]

Efficacy Results From GAD Studies of Venlafaxine XR

Results of the 2 short-term studies[23,24] showed that venlafaxine XR was significantly more effective than placebo and superior to buspirone. In the first study,[23] 349 subjects were evaluated: 96 received placebo and 86, 81, and 86 received venlafaxine XR at dosages of 75, 150, and 225 mg/day, respectively (titrated up to target dose over a 2-week period). Statistically significant differences from placebo in the HAM-A total score (Figure 1) were seen as early as week 1 in the 150 and 225 mg/day groups, although patients in these dosage groups were receiving only 75 mg/day at the week 1 timepoint. Significant differences compared with placebo in the reduction in the HAM-A total score were observed in at least one venlafaxine XR group at most other timepoints between week 1 and week 8 (see Figure 1).[23]

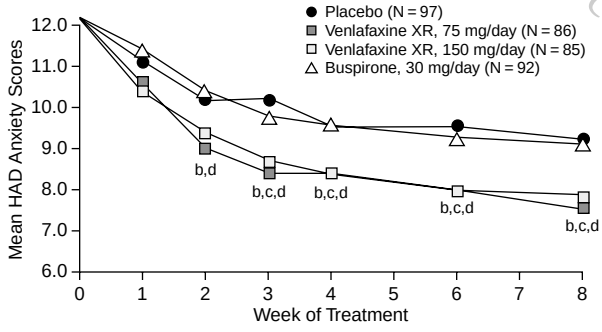
Additional outcome measures, such as the psychic anxiety factor and anxious mood item on the HAM-A, showed

Figure 1. Adjusted Mean Total HAM-A Scores (change from baseline) in Outpatients Treated With Venlafaxine XR (75, 150, or 225 mg/day) or Placebo for 8 Weeks[a]



[a]Adapted with permission from Haskins et al.[23]
[b]p = .05 for venlafaxine XR, 150 and 225 mg/day vs. placebo.
[c]p = .03 for venlafaxine XR, 75 and 225 mg/day vs. placebo.
[d]p = .03 for venlafaxine XR, 150 mg/day vs. placebo.
[e]p = .04 for venlafaxine XR, 150 and 225 mg/day vs. placebo.
[f]p = .03 for venlafaxine XR, 225 mg/day vs. placebo.

Figure 2. Mean Change in Hospital Anxiety and Depression (HAD) Anxiety Subscale Scores for Outpatients Treated With Venlafaxine XR (75 or 150 mg/day), Buspirone (30 mg/day), or Placebo for 8 Weeks[a]

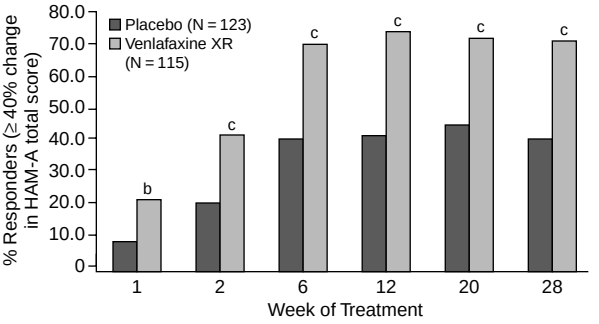


[a]Adapted with permission from Davidson et al.[24]
[b]p ≤ .05 for venlafaxine XR, 75 mg/day vs. placebo and buspirone.
[c]p ≤ .05 for venlafaxine XR, 150 mg/day vs. placebo.
[d]p ≤ .05 for venlafaxine XR, 150 mg/day vs. buspirone.

statistically significant improvements for all of the venlafaxine XR groups at week 1 and continuing at most timepoints throughout the study. The most robust improvements were seen with the highest dose.[23] Because these items are considered sensitive and specific indicators of anxiolytic response, and because they represent the cardinal features of GAD, they, in particular, highlight the efficacy of venlafaxine XR in the multiple domains of GAD.

In the second short-term, fixed-dose study,[24] efficacy data were available for 365 subjects: 98 assigned to placebo; 93 assigned to buspirone, 30 mg/day; 87 assigned to venlafaxine XR, 75 mg/day; and 87 assigned to venlafaxine XR, 150 mg/day. Significant improvements compared with placebo were seen in the HAM-A anxious mood and

Figure 3. Percentage of Outpatients Achieving Response (≥ 40% change from baseline in HAM-A scores) When Treated With Venlafaxine XR (75, 150, or 225 mg/day) or Placebo for 28 Weeks[a]



[a]Adapted with permission from Haskins et al.[25]
[b]p < .01 vs. placebo.
[c]p < .001 vs. placebo.

tension items and improvement measures with one or both of the doses of venlafaxine XR at most timepoints after week 1, and with both doses at week 8. In addition, venlafaxine XR, 75 mg/day, was significantly more effective than buspirone in reducing CGI severity scores at weeks 3, 4, and 8 and better than placebo at all timepoints after week 1. As shown in Figure 2, both venlafaxine XR doses produced statistically significantly better results than placebo on the anxiety subscale of the patient-rated Hospital Anxiety and Depression (HAD) scale at all timepoints after week 2 and were more effective than buspirone at all timepoints after week 1.[24]

The results of these short-term studies were extended in a study[25] evaluating flexible doses of venlafaxine XR over 6 months, showing that the benefits of venlafaxine XR therapy can be maintained over a long period in patients with GAD. In this study, 238 patients were evaluated on an intent-to-treat basis: 123 assigned to placebo and 115 assigned to venlafaxine XR at doses between 75 mg/day and 225 mg/day to control symptoms. Results of the HAM-A analysis showed that venlafaxine XR was statistically superior to placebo at all timepoints, beginning at week 1 and extending through the final on-therapy assessment at week 28.[25] Response rates based on a reduction in the HAM-A total score of ≥ 40% from baseline were also substantially higher with venlafaxine XR than with placebo beginning at week 1 (Figure 3). By week 2, 42% of venlafaxine XR–treated patients were considered to be responders compared with only 21% of placebo-treated patients. These response rates increased to approximately 69% at weeks 6 through 28 in the venlafaxine XR group compared with response rates of 42% to 46% in the placebo group.[25]

Preliminary results of a 6-month, fixed-dose study[26] of venlafaxine XR (37.5, 75, or 150 mg/day) compared with placebo support the long-term efficacy of venlafaxine XR in GAD. In this study, 544 nondepressed outpatients with

Table 2. Most Common (≥ 10% and at least twice the incidence with placebo) Short-Term and Long-Term Treatment-Emergent Adverse Events During Double-Blind Treatment With Venlafaxine XR for GAD[a]

	Short-Term (≤ week 8)		Long-Term (weeks 9–28)	
Adverse Event	Placebo (N = 127)	Venlafaxine XR (N = 124)	Placebo (N = 83)	Venlafaxine XR (N = 90)
Nausea	21	47	8	10
Somnolence	11	37	2	6
Dry mouth	11	25	2	4
Dizziness	14	19	2	21
Sweating	3	12	1	3
Constipation	3	11	1	2
Anorexia	3	11	2	1

[a]Adapted with permission from Haskins et al.[25] Data are percentages of patients.

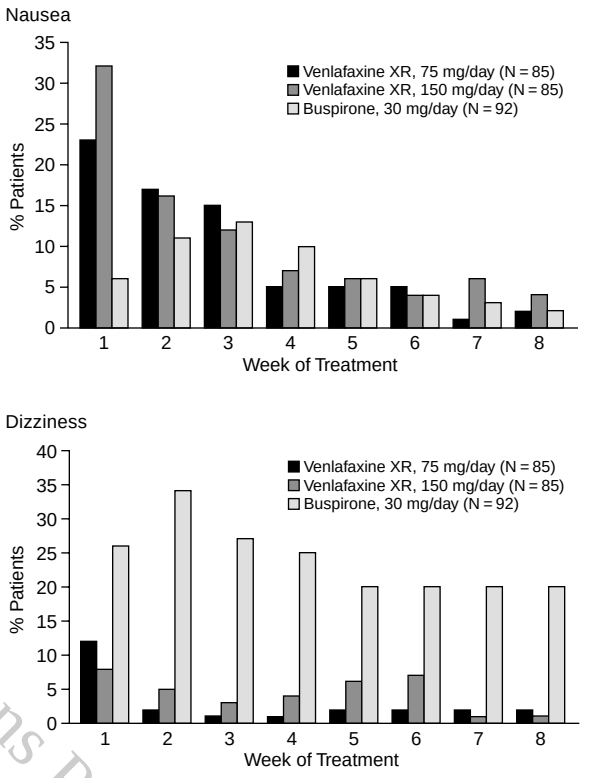
GAD with a minimum HAM-A baseline score of 20 (severe anxiety) were randomly assigned to one of the venlafaxine XR treatment groups or placebo. In addition to the standard outcome measures using the HAM-A and CGI, patients were assessed using the Social Adjustment Rating Scale. The venlafaxine XR–treated patients showed significant improvements compared with placebo recipients as early as week 1 (the 150-mg/day dose group) or week 2 (the 75-mg/day group); both groups were maintained consistently over the 6 months of the study. In addition, evaluation of Social Adjustment Rating Scale scores showed that the 2 higher doses of venlafaxine XR improved social adjustment compared with placebo.[26]

Taken together, these studies have demonstrated the anxiolytic efficacy of venlafaxine XR in the short and long term. The pooled effect size from these studies is 2.78, suggesting uncommon and substantial efficacy of venlafaxine XR in the treatment of GAD (references 23–26 and data on file, Wyeth-Ayerst Laboratories, 1998).

Safety Results From GAD Studies of Venlafaxine XR

The adverse events seen in patients with GAD treated with venlafaxine XR are similar to those reported in depression trials. As shown in Table 2, the most common adverse events during short-term treatment with venlafaxine XR are nausea, somnolence, dry mouth, dizziness, sweating, constipation, and anorexia.[25] The rate of these adverse events falls substantially during longer term therapy.[25] The drop in the incidence of adverse events over time is also illustrated in data taken from the short-term study comparing venlafaxine XR and buspirone (Figure 4) (data on file, Wyeth-Ayerst Laboratories, 1998). Consistent with what is seen in the clinic, venlafaxine XR–related nausea resolves rapidly after week 1 of treatment, with effects at 3 weeks and beyond similar to those produced by buspirone. Similar reductions in dizziness to approximately 5% with venlafaxine XR therapy were also seen in this study after week 1; in contrast, however, dizziness with buspirone treatment (30 mg/day), which occurred in approximately 20% of patients

Figure 4. Incidence of Nausea and Dizziness Over 8 Weeks of Treatment With Venlafaxine XR, 75 or 150 mg/day, or Buspirone, 30 mg/day, in Outpatients With GAD[a]



[a]Data on file, Wyeth-Ayerst Laboratories, 1998.

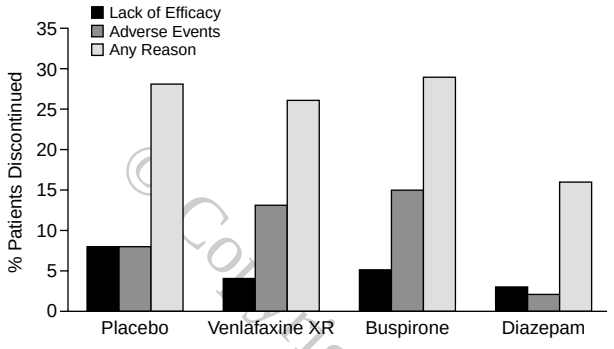
over the 8 weeks of the study, did not resolve substantially with continued treatment. This persistent adverse effect has implications for elderly patients, many of whom are treated with buspirone because of its putative favorable tolerability profile (data on file, Wyeth-Ayerst Laboratories, 1998).

Pooled data on short-term discontinuation rates with venlafaxine XR (Figure 5) support the findings of controlled trials in GAD, which showed good tolerability for this agent. Compared with that of placebo or buspirone, the discontinuation rate with venlafaxine XR from lack of efficacy was relatively low, comparable to that seen with diazepam (data on file, Wyeth-Ayerst Laboratories, 1998). The discontinuation rate due to adverse events was similar for venlafaxine XR and buspirone, although the percentage of patients who discontinued for any reason was somewhat lower with venlafaxine XR than with either buspirone or placebo. In aggregate, these findings suggest that venlafaxine XR is comparable to placebo and buspirone in tolerability.

CONCLUSIONS

In conclusion, venlafaxine XR is the most extensively evaluated antidepressant in the treatment of GAD. In addi-

Figure 5. Pooled Analysis of Short-Term Discontinuation Rates in 5 Placebo-Controlled Studies of Venlafaxine XR in Outpatients With GAD[a]



[a]Data on file, Wyeth-Ayerst Laboratories, 1998.

tion, the studies of venlafaxine XR in GAD excluded patients with major depression or other psychiatric disorders, providing strong support for the conclusion that its effects in this patient population are independent of its antidepressant activity and represent a "pure" anxiolytic effect. Furthermore, the robust efficacy of venlafaxine XR in treating patients with major depression and concomitant anxiety add considerable value to its use in GAD, since this patient population typically has high rates of associated depression. Finally, the effectiveness of venlafaxine XR is evident across a range of clinician and patient-rated outcome measures, including the gold standard of HAM-A, items of the HAM-A that represent the cardinal features of GAD (such as the anxious mood and tension factors), the HAD, and the CGI. Venlafaxine XR is the first antidepressant to also be indicated for the treatment of GAD, an important contribution to the armamentarium of therapy for this anxiety disorder.

Drug names: buspirone (BuSpar), diazepam (Valium and others), fluoxetine (Prozac), venlafaxine XR (Effexor XR).

REFERENCES

1. Lecrubier Y, Hergueta T. Differences between prescription and consumption of antidepressants and anxiolytics. Int Clin Psychopharmacol 1998; 13(suppl 2):S7–S11
2. Katon W, Von Korff M, Lin E, et al. Distressed high utilizers of medical care: DSM-III-R diagnoses and treatment needs. Gen Hosp Psychiatry 1990;12:355–362
3. Johnson MR, Emmanuel N, Crawford M, et al. Treatment of generalized anxiety disorder with venlafaxine: a series of 11 cases. J Clin Psychopharmacol 1998;18:418–419
4. Geracioti TD Jr. Venlafaxine treatment of panic disorder: a case series. J Clin Psychiatry 1995;56:408–410
5. Papp LA, Sinha SS, Martinez JM, et al. Low-dose venlafaxine treatment in panic disorder. Psychopharmacol Bull 1998;34:207–209
6. Pollack MH, Worthington JJ III, Otto MW, et al. Venlafaxine for panic disorder: results from a double-blind, placebo-controlled study. Psychopharmacol Bull 1996;32:667–670
7. Kelsey JE. Venlafaxine in social phobia. Psychopharmacol Bull 1995;31: 767–771
8. Ananth J, Burgoyne K, Smith M, et al. Venlafaxine for treatment of obsessive-compulsive disorder [letter]. Am J Psychiatry 1995;152:1832
9. Grossman R, Hollander E. Treatment of obsessive-compulsive disorder with venlafaxine. Am J Psychiatry 1996;153:576–577
10. Yaryura-Tobias JA, Neziroglu FA. Venlafaxine in obsessive-compulsive disorder [letter]. Arch Gen Psychiatry 1996;53:653–654
11. Zajecka JM, Fawcett J, Guy C. Coexisting major depression and obsessive-compulsive disorder treated with venlafaxine [letter]. J Clin Psychopharmacol 1990;10:152–153
12. Rauch SL, O'Sullivan RL, Jenike MA. Open treatment of obsessive-compulsive disorder with venlafaxine: a series of ten cases [letter]. J Clin Psychopharmacol 1996;16:81–84
13. Ninan PT, Knight B, Kirk L, et al. A controlled trial of venlafaxine in trichotillomania: interim phase I results. Psychopharmacol Bull 1998;34: 221–224
14. Gould RA, Otto MW, Pollack MH. A meta-analysis of treatment outcome for panic disorder. Clin Psychol Rev 1995;15:819–844
15. Jenike MA, Hyman S, Baer L, et al. A controlled trial of fluvoxamine in obsessive-compulsive disorder: implications for a serotonergic theory. Am J Psychiatry 1990;147:1209–1215
16. Khan A, Upton GV, Rudolph RL, et al. The use of venlafaxine in the treatment of major depression and major depression associated with anxiety: a dose-response study. J Clin Psychopharmacol 1998;18:19–25
17. Feighner JP, Entsuah AR, McPherson MK. Efficacy of once-daily venlafaxine extended release (XR) for symptoms of anxiety in depressed outpatients. J Affect Disord 1998;47:55–62
18. 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
19. 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
20. Clayton PJ, Grove WM, Coryell W, et al. Follow-up and family study of anxious depression. Am J Psychiatry 1991;148:1512–1517
21. Fawcett J, Scheftner WA, Fogg L, et al. Time-related predictors of suicide in major affective disorder. Am J Psychiatry 1990;147:1189–1194
22. 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
23. Haskins T, Rudolph R, Pallay A, et al. Double-blind, placebo-controlled study of once daily venlafaxine XR in outpatients with generalized anxiety disorder (GAD). Presented at the 21st meeting of the Collegium International Neuro-Psychopharmacologicum; July 12–16, 1998; Glasgow, Scotland
24. 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
25. Haskins JT, Rudolph R, Aguiar L, et al. Venlafaxine XR is an efficacious short- and long-term treatment for generalized anxiety disorder. Presented at the 11th annual meeting of the European College of Neuropsychopharmacology; Oct 31–Nov 4, 1998; Paris, France
26. Hackett D, Parks V, Salinas E. A 6 month evaluation of 3 dose levels of venlafaxine extended-release in non-depressed outpatients with generalized anxiety disorder. Presented at the 19th annual conference of the Anxiety Disorders Association of America; March 25–28, 1999; San Diego, Calif