Efficacy of Venlafaxine Extended-Release Capsules in Nondepressed Outpatients With Generalized Anxiety Disorder
A 6-Month Randomized Controlled Trial

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Context  Generalized anxiety disorder (GAD) is a chronic disorder that is associated with debilitating psychic and somatic symptoms. Venlafaxine extended-release (XR) capsules have been shown to be effective in short-term treatment of patients with GAD without major depressive disorder (MDD), but long-term data are needed to establish whether this agent confers persistent benefits.

Objective  To compare the 6-month efficacy and safety of a flexible dosage of venlafaxine XR in outpatients with GAD without associated MDD.


Setting  Fourteen outpatient clinics and private psychiatric practices in the United States.

Participants  A total of 251 outpatients aged 18 years or older who met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for GAD, had sufficient symptoms to require treatment, and did not have coexisting MDD.

Interventions  Participants were randomly assigned to receive either placebo (n=127) or venlafaxine XR (75, 150, or 225 mg/d, as required to control symptoms; n=124) for 28 weeks.

Main Outcome Measures  Changes from baseline in the Hamilton Rating Scale for Anxiety (HAM-A) total score, the HAM-A psychic anxiety factor score, and the Clinical Global Impressions (CGI) scale Severity of Illness and Global Improvement scores, compared by intervention group.

Results  During weeks 6 through 28, response rates in the venlafaxine XR group were 69% or higher compared with rates of 42% to 46% in the placebo group (P<.001). By an evaluable-patient analysis, venlafaxine XR compared with placebo significantly improved anxiety scores from week 1 or 2 through week 28 on all primary efficacy measures, including the HAM-A total (P<.001), the HAM-A psychic anxiety factor (P<.001), and the CGI scale scores (P<.001). Adjusted mean changes from baseline to week 28 using last-observation-carried-forward methods were for HAM-A, venlafaxine XR −13.4, placebo −8.7 (P<.001); for HAM-A psychic anxiety score, venlafaxine XR −7.4, placebo −4.2 (P<.001); and for CGI-Improvement, venlafaxine XR 2.2, placebo 3.0 (P<.001). The most common treatment-emergent adverse event was nausea, followed by somnolence and dry mouth.

Conclusions  This study is the first placebo-controlled demonstration of the long-term efficacy of any drug class in treating outpatients with DSM-IV–diagnosed GAD. Venlafaxine XR is an effective, rapidly acting, safe, once-daily agent for both the short-and long-term treatment of anxiety and may provide an important alternative to currently available anxiolytics.
Primary care practitioners play central roles in caring for patients with GAD. Patients manifesting somatic symptoms of GAD, such as chronic headaches, palpitations, sweating, frequent urination, and even irritable bowel syndrome,\(^7\) are more likely to present first to the primary care physician. Such findings may account for the high use of medical resources among patients with GAD.\(^8,9\) In addition, patients have a higher risk of negative outcomes (eg, increased burden on the health care system, increased morbidity and mortality rates) if the underlying GAD is not treated.\(^10-12\) Of particular concern to the primary care practitioner is the effect of GAD on quality of life. Massion et al\(^13\) found that GAD was associated with diminished overall emotional health and identified evidence of decreased employment and corresponding increased reliance on public assistance, impaired social life (eg, limited friendships or few recreational activities), and low ratings of life satisfaction. These data supported those obtained from the Epidemiologic Catchment Area study,\(^14,15\) suggesting that GAD is associated with significant psychosocial impairment and a significant negative effect on quality of life.

The current US Food and Drug Administration–approved agents for the treatment of anxiety include the benzodiazepines and buspirone.\(^16\) Although well-controlled data are lacking, long-term benzodiazepine use for the treatment of GAD may be associated with risks of tolerance, abuse, and dependence. Although buspirone is effective in the treatment of GAD and avoids the disadvantages associated with benzodiazepines, it has a slower onset of action—typically 1 to 3 weeks. Furthermore, buspirone is associated with a limited spectrum of efficacy and a low level of patient satisfaction.\(^16\) Tricyclic antidepressants and newer classes of antidepressants, including paroxetine and nefazodone, have also been evaluated in anxiety disorders, including a small number of studies in GAD, but data are, in some cases, complicated by the inclusion of patients with major depression\(^7,17-19\) or the absence of a placebo control.\(^20\)

Among the newer antidepressants, only venlafaxine extended-release (XR) has been shown to possess unequivocal efficacy in GAD. The anxiolytic efficacy of venlafaxine XR has been demonstrated in 2 clinical studies in a defined population of patients with GAD without associated MDD.\(^21,22\) Because GAD is a chronic disorder, long-term data were needed to assess fully the safety and efficacy of venlafaxine XR for the treatment of this disorder. Despite the chronic nature of GAD, there are to date no published placebo-controlled studies demonstrating that pharmacologic therapy provides long-term (ie, >3 months) efficacy in DSM-IV–diagnosed GAD.

**METHODS**

**Study Design**

This study was a 6-month, randomized, double-blind, placebo-controlled, parallel-group trial in nondepressed outpatients with GAD conducted at 14 centers (outpatient clinics and private psychiatric practices) in the United States. The study was conducted from May 1996 through October 1997. Approximately 125 patients were enrolled in each treatment group to achieve 90% power to detect a 4-point difference in the Hamilton Rating Scale for Anxiety (HAM-A) total score between the groups using a 2-sided test to determine statistical significance. After a 4- to 10-day prestudy screening period, patients meeting the entry criteria were assigned randomly to 1 of 2 treatment groups: venlafaxine XR (75, 150, or 225 mg/d or matching placebo). No additional dosage increases beyond 225 mg/d were allowed. Dosage reduction to improve tolerability for the study drug was allowed to a minimum dosage of 75 mg/d. Patients were seen at the screening and baseline visits, after randomization at weekly intervals during the first month (study days 7, 14, 21, and 28), at biweekly intervals during the second month (study days 42 and 56), and at monthly intervals during the remainder of the double-blind phase (study days 84, 112, 140, 168, and 196). Patients also were seen once for a poststudy visit 4 to 10 days after dosage tapering.

**Patient Selection**

Outpatients 18 years or older with MDD who met the criteria for GAD as defined in the DSM-IV and who were sufficiently symptomatic to require treatment were eligible for inclusion in the study. Patients were required to have screening and baseline total scores of at least 18 on the HAM-A and scores of at least 2 on items 1 (anxious mood) and 2 (tension). However, patients who had a reduction of at least 20% in the HAM-A total score between the screening visit and the baseline visit were not eligible. Other inclusion criteria included a total score of at least 9 on the Raskin Depression Scale at screening and baseline and a Covi Anxiety Scale score greater than the total score on the Raskin Depression Scale. The institutional review board of each study center reviewed and approved the study protocol, and written informed consent was obtained from each patient before study enrollment.

To permit the study of the purely anxiolytic effects of venlafaxine XR in patients with GAD, patients with a recent history (within 6 months of study entry) or a current diagnosis of MDD (according to DSM-IV criteria) were ex-
encluded. The absence of MDD was confirmed using a structured interview at the screening visit. Patients also were excluded if they had a history or presence of any psychotic illness, bipolar disorder, antisocial personality or other severe Axis II disorder, or if they had a clinically significant psychiatric disorder other than GAD. Additionally, patients with a Raskin Depression Scale score greater than 3 on any single item or a Covi Anxiety Scale score greater than 4 for somatic symptoms were excluded (we hypothesized a priori that venlafaxine XR would affect psychic symptoms predominantly, so patients with severe somatic symptoms were excluded).

Other exclusion criteria included treatment with venlafaxine (immediate-release or XR) within 6 months of study day 1; the use of any investigational drug or procedure, any antipsychotic drug, fluoxetine, sumatriptan, or the regular use of a benzodiazepine or electroconvulsive therapy within 30 days of study day 1; or any use of an anxiolytic or any antidepressant (other than fluoxetine) within 14 days of study day 1. Patients also were excluded if they had used any sedative hypnotic drug (other than chloral hydrate) or any other psychotropic drug or substance not specified above within 7 days of double-blind treatment or if they had taken a nonpsychopharmacologic substance with psychotropic effects within 7 days of double-blind treatment, unless a stable dose had been maintained for at least 3 months prior to study day 1. Patients were allowed to take chloral hydrate (as much as 1000 mg at bedtime no more than 4 times per week) through study day 21 if needed for sleep. Women who were pregnant or lactating were excluded from the study, as were women of childbearing potential not using a medically acceptable form of contraception.

**Study Procedures**

Study candidates underwent a complete evaluation at the screening visit, including a medical and psychiatric history, routine physical examination, laboratory determinations, and 12-lead electrocardiography. Evaluations using the HAM-A and Covi and Raskin scales also were performed at this time. Between 4 and 10 days following the initial screening visit, patients who met all study entry criteria returned for a baseline visit, at which assessments with the HAM-A and Covi and Raskin scales were repeated. Patients meeting the entry criteria at both the screening and baseline visits were then entered into the study and randomly assigned to the venlafaxine XR or placebo groups. Adverse events, compliance, efficacy, and vital signs were evaluated at each visit.

The statistical analyses were performed by the Biostatistics Section of Wyeth-Ayerst Research. The content of this article was developed by its authors in collaboration with Wyeth-Ayerst Research.

**Efficacy**

The primary efficacy variables were the HAM-A total score, the HAM-A psychic anxiety factor score, and the Clinical Global Impressions (CGI) scale Severity of Illness and Global Improvement scores. The anxiolytic effects of venlafaxine XR were determined by comparing the differences between treatment groups on the scores for each of the primary efficacy variables at baseline and on subsequent evaluation days. A patient was considered a responder to treatment if the HAM-A total score decreased by at least 40% from baseline or if the score on CGI-Global Improvement was 1 (very much improved) or 2 (much improved).

Secondary efficacy variables were the HAM-A somatic anxiety factor score, the Hospital Anxiety and Depression anxiety subscale score, and the Covi Anxiety Scale score. Final ratings for efficacy were done on the last day the patients took a full dose of study medication (ie, before dosage tapering) or as soon as possible thereafter but not more than 3 days after the last dose.

**Safety**

Safety was evaluated on the basis of reports of study events and the results of routine physical examinations, laboratory determinations, and electrocardiography. Study events were identified from spontaneous patient reports as well as from nonspecific questioning by study site personnel.

**Statistical Analyses**

Efficacy analyses were done on an evaluable-patient basis, which included all patients who had a baseline evaluation and at least 1 evaluation on at least 1 of the primary efficacy variables during the double-blind treatment phase or within 3 days of terminating treatment with the study drug. Data from this evaluable-patient population were evaluated by both observed-cases (OC) and last-observation-carried-forward (LOCF) methods. For the OC analysis, all efficacy ratings collected were analyzed. For the LOCF analysis, the previous rating for a patient who missed a scheduled evaluation or who withdrew before scheduled study completion was carried forward into all subsequent time slots for which actual (observed) rating results were not available. The responder rates between treatment groups were examined at each point using the Fisher exact test.

Changes from baseline for the HAM-A total, HAM-A psychic and somatic anxiety factors, Hospital Anxiety and Depression anxiety subscale, CGI-Severity of Illness, and Covi Anxiety Scale scores were assessed using a 2-way analysis of covariance, with treatment and investigator as main effects and baseline scores as the covariates. The CGI-Global Improvement item was analyzed using an analysis of variance with no baseline covariate. All tests of hypotheses were 2-sided and were significant at $P\leq.05$.

**RESULTS**

**Patient Characteristics**

A total of 261 patients are included in the database. Ten of these were considered “no data” patients as they were randomized to treatment and dispensed study drugs but were lost to follow-up and did not provide any data after inclusion. Of the remaining 251 patients who were enrolled and for whom baseline data were collected, 127 received placebo and 124 received venlafaxine XR; 13 patients had...
no primary evaluations while receiving therapy or within 3 days of study drug discontinuation. Of 238 patients in the evaluable-patient population, 123 received placebo and 115 received venlafaxine XR. The baseline demographics and clinical characteristics of the evaluable patients are shown in Table 1, and patient disposition is shown in Figure 1. There were no significant differences between groups. All patients received at least 1 dose of either venlafaxine XR or placebo, and approximately half the patients in the venlafaxine XR group received the drug for 28 weeks or longer. During treatment, 29% (36/124) of patients in the venlafaxine XR group received mean doses of 0 to 100 mg/d, 61% (76/124) received 101 to 200 mg/d, and 10% (12/124) received more than 200 mg/d. Patients taking placebo ingested more capsules per day (median range to high range) than patients taking venlafaxine XR (13.4% vs 9.7%, respectively, ingested a mean >2.7 capsules daily; 65.4% vs 61.3%, respectively, ingested ≥1.3 to ≤2.7 capsules daily; and 21.6% vs 29.0%, respectively, ingested ≥1.3 capsules daily).

Chloral hydrate was taken by 6 patients (4.8%) given venlafaxine XR and by 3 (2.4%) given placebo. Of the 251 patients, 147 (59%) withdrew from treatment during the double-blind phase. Primary reasons for premature withdrawal included unsatisfactory response, with significantly less attrition in the venlafaxine XR group than in the placebo group (10 [8%] vs 28 [22%]; \(P = .002\)); adverse reaction, with the placebo group showing significantly less attrition than the venlafaxine XR group (18 [14%] vs 30 [24%]; \(P = .05\)); and failure to return (any reason) with significantly less attrition in the venlafaxine XR group (10 [8%] vs 22 [17%]; \(P = .04\)). Secondary reasons are shown in Figure 1.

**Anxiolytic Response**

The efficacy analysis was conducted on data from the 238 patients in the evaluable-patient population: 123 in the placebo group and 115 in the venlafaxine XR group.

Adjusted mean changes from baseline to week 28 using LOCF methods were: for HAM-A, venlafaxine XR −13.4, placebo −8.7 (\(P < .001\)); for HAM-A psychic anxiety score, venlafaxine XR −7.4, placebo −4.2 (\(P < .001\)); and for CGI-Improvement, venlafaxine XR 2.2, placebo 3.0 (\(P < .001\)). Changes from baseline in the HAM-A total score are shown in Figure 2. As early as week 1, patients treated with venlafaxine XR had significant (\(P < .01\)) reductions in scores compared with patients treated with placebo when all patients assigned to the venlafaxine XR group received 75 mg/d. Figure 2 shows the adjusted mean total scores on the HAM-A scale by week. Significant (\(P < .001\)) differences between patients receiving venlafaxine XR and those receiving placebo were maintained through the final assessment of patients receiving therapy (week 28). Similar results were seen for the HAM-A psychic anxiety factor scores (Figure 2), in which patients treated with venlafaxine XR had significant reductions from baseline scores compared with patients treated with placebo at week 1 (\(P = .02\)) and at weeks 2 through 28 (\(P < .001\)).

### Table 1. Demographic and Clinical Characteristics of Evaluable Patients at Baseline

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 123)</th>
<th>Venlafaxine XR (n = 115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>38 (11)</td>
<td>41 (12)</td>
</tr>
<tr>
<td>Race, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>116 (94)</td>
<td>102 (89)</td>
</tr>
<tr>
<td>Hispanic American</td>
<td>0 (0)</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Asian American</td>
<td>2 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>African American</td>
<td>4 (3)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Male</td>
<td>51 (41)</td>
<td>47 (41)</td>
</tr>
<tr>
<td>Female</td>
<td>72 (59)</td>
<td>68 (59)</td>
</tr>
<tr>
<td>Weight, mean (SD), kg</td>
<td>77.4 (18.9)</td>
<td>74.7 (14.4)</td>
</tr>
<tr>
<td>Duration of current episode, mean (SD), wk</td>
<td>323 (437)</td>
<td>392 (577)</td>
</tr>
<tr>
<td>HAM-A total score, mean (SD)</td>
<td>25.0 (5)</td>
<td>25.0 (5)</td>
</tr>
<tr>
<td>HAM-A psychic anxiety factor score, mean (SD)</td>
<td>14.0 (2)</td>
<td>14.0 (2)</td>
</tr>
<tr>
<td>CGI-Severity of illness score, No. (%)(\geq 4)</td>
<td>78 (63)</td>
<td>76 (66)</td>
</tr>
<tr>
<td>CGI-Severity of illness score, No. (%)(&lt; 4)</td>
<td>44 (36)</td>
<td>38 (33)</td>
</tr>
</tbody>
</table>

*XR indicates extended-release; HAM-A, Hamilton Rating Scale for Anxiety; and CGI, Clinical Global Impressions. Percentages may not add to 100% because of rounding.†Moderate illness is denoted by a score of 4 and mild illness by a score of 3.

**Figure 1. Study Flow Diagram**

261 Patients Enrolled

251 Randomized

127 Assigned to Placebo

124 Assigned to Venlafaxine XR

123 Evaluable for Efficacy Analysis

4 No Primary Efficacy Evaluation

83 Withdrawn

28 Unsatisfactory Response

18 Adverse Event

22 Failure to Return

4 Patient Request

4 Protocol Violation

0 Other Medical Event

7 Other Nonmedical Event

44 Completed Trial

115 Evaluable for Efficacy Analysis

9 No Primary Efficacy Evaluation

64 Withdrawn

10 Unsatisfactory Response

30 Adverse Event

10 Failure to Return

6 Patient Request

3 Protocol Violation

1 Other Medical Event

4 Other Nonmedical Event

60 Completed Trial

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In the assessment of CGI-Severity of Illness scores (Figure 2), the adjusted mean scores were significantly lower in the venlafaxine XR group than in the placebo group at weeks 2 through 4 ($P<.01$), with a wider separation of scores occurring at weeks 6 through 28 ($P<.001$). The venlafaxine XR group was also superior to the placebo group on the CGI-Global Improvement item at all points assessed beyond week 1 (scores at week 28 of the study are presented in Table 2). Similar results were found in the analysis of secondary efficacy variables. The adjusted mean scores for the Hospital Anxiety and Depression anxiety subscale were significantly reduced in the venlafaxine XR group compared with the placebo group at both week 8 and week 28 ($P<.001$). Analysis of the Covi Anxiety Scale at weeks 8 and 28 showed similar results. Beginning at week 1, the adjusted mean scores for the anxious mood and tension items of the HAM-A scale were significantly lower in the venlafaxine XR group than in the placebo group. These advantages were maintained throughout the study. For the HAM-A somatic factor, adjusted mean scores of the evaluable-patient population by LOCF analysis were significantly ($P<.05$) lower in the venlafaxine XR group than in the placebo group at all points from weeks 1 through 28.

Response to treatment was defined as either a reduction in HAM-A total score of at least 40% from baseline or a CGI-Global Improvement score of 1 or 2. The response rates of patients treated with venlafaxine XR, as assessed by reduction in HAM-A total score, were significantly better than those of patients receiving placebo (Figure 3). By week 2, 42% of patients in the venlafaxine XR group could be categorized as responders compared with only 21% of patients in the placebo group ($P<.001$). During weeks 6 through 28, response rates in the venlafaxine XR group were 69% or higher compared with rates of 42% to 46% in the placebo group ($P<.001$). Similar results were observed for CGI-Global Improvement, with significantly more patients treated with venlafaxine XR responding than patients receiving placebo at each evaluation except week 1.

Finally, for all efficacy measures, there was a high degree of concordance between the results obtained using LOCF analyses vs OC analyses. Analysis of these same efficacy variables using the OC method resulted in identical or better results than those observed with the LOCF.
Abnormal ejaculation or orgasm was spontaneously reported in 0% and 20% of male patients and abnormal orgasm in 0% and 1% of female patients receiving placebo and venlafaxine XR, respectively. Anorgasmia was spontaneously reported in 2% and 20% of male patients and in 0% and 8% of female patients receiving placebo and venlafaxine XR, respectively. These events, however, resulted in withdrawal from the study by 1% and 2% of the patients receiving placebo and venlafaxine XR, respectively.

The significant anxiolytic response to venlafaxine XR was maintained during the entire 6 months of the study. Improvements in all primary and secondary assessments between weeks 2 and 28 were highly significant for venlafaxine XR compared with placebo. These findings are important, given the

### Safety

The adverse events in this study were generally consistent with those reported in the labeling for the immediate-release and XR forms of venlafaxine (Table 3). The most common treatment-emergent adverse events with venlafaxine XR (occurring in ≥10% of patients and at a rate at least twice that of patients taking placebo) during the short term (≤56 days) were anorexia, constipation, dizziness, dry mouth, nausea, sexual dysfunction, somnolence, and sweating. With continued therapy during the long term (>56-196 days), most of these adverse events subsided. Adverse events were cited as a reason for discontinuation by 17% and 26% of the placebo and venlafaxine XR–treated patients, respectively.

Supine pulse rates for the venlafaxine XR group showed small but significant increases from baseline, ranging from 2.0 to 5.3/min throughout and after the study. The final mean change for patients receiving venlafaxine XR (3.2/min), however, was not significantly different from that of placebo. Mean supine diastolic blood pressure values for venlafaxine XR showed few significant changes (≤2.4 mm Hg) from baseline. Throughout and after the study, small changes in mean supine diastolic blood pressure (−0.1 to 2.4 mm Hg) for venlafaxine XR were significantly different compared with mean changes for placebo (−1.2 to −3.0 mm Hg). Elevated blood pressure, however, was the reason for discontinuation in only 1% and 4% of the placebo and venlafaxine XR groups, respectively.

### Table 2. Distribution of CGI-Global Improvement Scores at End of Study (Week 28)*

<table>
<thead>
<tr>
<th>No. (%) of Patients by Score</th>
<th>Placebo (n = 127)</th>
<th>Venlafaxine XR (n = 124)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17 (14)</td>
<td>42 (37)</td>
</tr>
<tr>
<td>2</td>
<td>23 (19)</td>
<td>35 (30)</td>
</tr>
<tr>
<td>3</td>
<td>37 (30)</td>
<td>19 (17)</td>
</tr>
<tr>
<td>4</td>
<td>32 (26)</td>
<td>12 (10)</td>
</tr>
<tr>
<td>5</td>
<td>11 (9)</td>
<td>6 (5)</td>
</tr>
<tr>
<td>6</td>
<td>2 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Total</td>
<td>122†</td>
<td>115†</td>
</tr>
</tbody>
</table>

*CGI indicates Clinical Global Impressions; XR, extended-release; total score (evaluable-patient population and last-observation-carried-forward analysis).

### Table 3. Most Common Treatment-Emergent Adverse Events During Double-Blind Treatment*<br>

<table>
<thead>
<tr>
<th>No. (%) of Patients</th>
<th>Placebo (n = 127)</th>
<th>Venlafaxine XR (n = 124)</th>
<th>Placebo (n = 83)</th>
<th>Venlafaxine XR (n = 90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>27 (21)</td>
<td>58 (47)</td>
<td>7 (8)</td>
<td>9 (10)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>14 (11)</td>
<td>46 (37)</td>
<td>2 (2)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>14 (11)</td>
<td>31 (25)</td>
<td>2 (2)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>18 (14)</td>
<td>24 (19)</td>
<td>2 (2)</td>
<td>19 (21)</td>
</tr>
<tr>
<td>Sweating</td>
<td>4 (3)</td>
<td>15 (12)</td>
<td>1 (1)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Constipation</td>
<td>4 (3)</td>
<td>14 (11)</td>
<td>1 (1)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Sexual dysfunction (male)†</td>
<td>0 (0)</td>
<td>14 (29)</td>
<td>1 (2)</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>4 (3)</td>
<td>14 (11)</td>
<td>2 (2)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

*Adverse events occurring in at least 10% of patients at a rate at least twice that of patients taking placebo.

†On the basis of the number of men (n = 52 for placebo and venlafaxine extended-release [XR], respectively).

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chronic nature of GAD and the risks during long-term treatment associated with other available interventions. Long-term pharmacologic therapies that have a convenient dosing schedule (ie, once daily) and established efficacy may improve significantly the quality of life of patients with GAD. Once-daily dosing also may improve patients’ compliance with treatment.

In this study, the adverse events that occurred during treatment with venlafaxine XR were generally mild to moderate and tended to subside with continued therapy. Nevertheless, the aggressive titration schedule may have exaggerated the incidence of adverse events. A slower titration schedule, such as that described in the approved labeling for venlafaxine XR, may produce tolerability and reduce the rate of discontinuation observed in this study. Most of the analyses in this study used the LOCF method (except for the use of the OC analysis illustrated in Figure 2, A); therefore, the rate of discontinuation (approximately 59%) only becomes apparent in the OC analysis. The OC analysis may have more significance than the LOCF analysis because it takes into account those control patients whose adequate response to treatment enabled them to remain in the trial. The degree of response exhibited by the patients who continued taking venlafaxine XR vs that of those taking placebo is therefore an important consideration, and demonstration of efficacy by way of the OC analysis may enable us to distinguish the pharmacologic effect of venlafaxine XR from the nonspecific effects (including spontaneous recovery) observed in the placebo group.

Venlafaxine XR is a safe, effective treatment for outpatients with GAD and improves both the psychic and somatic symptoms associated with GAD. This placebo-controlled study demonstrated that pharmacologic therapy can produce long-term (6-month) efficacy in treating outpatients meeting DSM-IV criteria for GAD and has important implications for the pharmacologic management of GAD.

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