Venlafaxine Extended Release vs Placebo and Paroxetine in Social Anxiety Disorder

Michael R. Liebowitz, MD; Alan J. Gelenberg, MD; Dennis Munjack, MD

Background: Evidence indicates that venlafaxine hydrochloride extended release (ER) effectively ameliorates anxiety symptoms.

Objectives: To evaluate the efficacy, safety, and tolerability of flexible-dose venlafaxine ER compared with placebo in the short-term treatment of generalized social anxiety disorder and, secondarily, to compare paroxetine with venlafaxine ER and paroxetine with placebo.

Design: Adult outpatients with DSM-IV generalized social anxiety disorder for 6 months or longer were randomly assigned to receive venlafaxine hydrochloride ER (75-225 mg/d), paroxetine (20-50 mg/d), or placebo for 12 weeks or less at 26 centers in the United States. The primary outcome measure was the total Liebowitz Social Anxiety Scale score. Secondary measures included response (Clinical Global Impression–Improvement score, 1 or 2) rates and Clinical Global Impression–Severity of Illness and Social Phobia Inventory scores.

Results: Of 440 patients treated, 413 (93.9%) were included in the last-observation-carried-forward efficacy analysis; of the 429 patients in the safety population, 318 (74.1%) completed the study. Mean daily doses were 201.7 mg (SD, 38.1 mg) of venlafaxine hydrochloride ER and 46.0 mg (SD, 7.9 mg) of paroxetine. Venlafaxine ER treatment was significantly superior to placebo at weeks 1 through 12 on the Liebowitz Social Anxiety Scale and Social Phobia Inventory and at week 2 and weeks 6 through 12 for Clinical Global Impression–Severity of Illness and responder status, and was significantly superior to paroxetine treatment at weeks 1 and 2 for the Social Phobia Inventory (P < .05 for all). Paroxetine treatment was significantly superior to placebo at weeks 3 through 12 on the Liebowitz Social Anxiety Scale, the Clinical Global Impression–Severity of Illness scale, and the Social Phobia Inventory, and at weeks 4 through 12 for response (P < .05 for all). Week 12 response rates were significantly greater for the venlafaxine ER and paroxetine groups (58.6% and 62.5%, respectively) vs the placebo group (36.1%) (P < .001 for both).

Conclusion: Venlafaxine ER is effective in the short-term treatment of generalized social anxiety disorder, with efficacy and tolerability comparable to paroxetine.

Arch Gen Psychiatry. 2005;62:190-198

Social Anxiety Disorder (SAD) is a common and frequently disabling illness, characterized by excessive and persistent fear and avoidance of social situations, according to the DSM-IV. Social anxiety disorder extends beyond common shyness, causing patients to avoid feared situations or to endure them with intense anxiety and distress, resulting in significantly impaired psychosocial functioning. Although the nongeneralized subtype of the disorder is limited to one or a few situations (e.g., public speaking), generalized SAD is associated with fear and avoidance of a wide variety of social situations.

With 12-month and lifetime prevalence estimates of 7.9% and 13.3%, respectively, SAD is one of the most common psychiatric disorders. Data from the National Comorbidity Survey indicate that SAD is the most common of the anxiety disorders and the third most common psychiatric diagnosis after major depressive disorder and alcohol dependence.

In contrast to many other psychiatric disorders, SAD begins early in life. The mean age of onset is approximately 15 years, and the illness infrequently occurs past the age of 25 years. A high rate of psychiatric comorbidity is associated with SAD, with estimates ranging from 43% in a managed care population to 69% in community samples. In most patients with comorbid SAD, the onset of SAD preceded that of the comorbid diagnosis.

Social anxiety disorder tends to follow a long-term and unremitting course, and is rarely resolved without treatment. However, patients often do not seek treatment from a mental health clinician for many years, if at all. More often, individuals present to a primary care
clinician with symptoms related to psychological comorbidities or general medical complaints, and the symptoms of SAD remain unrecognized. Consequently, patients endure years of disability and a significantly impaired quality of life. All domains of psychosocial functioning are affected, limiting academic performance and work productivity, interfering with family life and leisure activities, and hindering the ability to form and maintain relationships. The sobering individual and societal burden of SAD underscores the need for continued research into effective medication and cognitive behavioral treatments for this disorder.

A greater understanding of the neurobiological underpinnings of SAD may be the key to optimizing treatment strategies. Knowledge of brain mechanisms involved in SAD is rather limited, but available data suggest the involvement of the serotonergic, dopaminergic, and possibly noradrenergic systems. Several lines of evidence support serotonergic and dopaminergic dysfunctions in patients with SAD compared with control subjects. Data on noradrenergic function in patients with SAD are inconsistent. An early study that included a mixed population of patients with either specific or generalized SAD found significantly elevated plasma norepinephrine levels in the patients with SAD compared with controls. Later studies, however, found no significant differences in noradrenergic indexes in patients with generalized SAD. Although one study did find greater sympathetic arousal in patients with nongeneralized disease compared with those with the generalized subtype and healthy controls. Further investigation is needed to determine the role of the noradrenergic system in those with generalized SAD.

Consistent with what is known about the pathophysiological features of the disorder, a growing body of evidence suggests that antidepressants, in particular those that affect serotonergic or dopaminergic neurotransmission, are efficacious in the treatment of generalized SAD. Randomized double-blind investigations of treatment with the monoamine oxidase inhibitor phenelzine sulfate established its efficacy in patients with generalized SAD, and results suggest it was superior not only to placebo but also to atenolol and psychotherapy. The promising results with phenelzine encouraged investigations of the reversible inhibitor of monoamine oxidase A, moclobemide. These trials produced mixed results, however, with early studies demonstrating significant improvement compared with placebo, while later studies failed to confirm efficacy.

The selective serotonin reuptake inhibitors have demonstrated efficacy superior to placebo in treating this disorder and offer a treatment option with fewer safety and tolerability concerns compared with the monoamine oxidase inhibitors. While selective serotonin reuptake inhibitors principally act via serotonergic mechanisms, they do have indirect effects on dopamine, which may be relevant to SAD.

It is clear from this extensive body of evidence that serotonergic drugs are effective for reducing anxiety in patients with SAD. Evidence has shown that the serotonin-norepinephrine reuptake inhibitor venlafaxine hydrochloride extended release (ER) is also effective for ameliorating symptoms of anxiety, including generalized anxiety disorder, symptoms of anxiety in patients with major depressive disorder, and comorbid major depressive disorder and generalized anxiety disorder. This study is one of a series of studies designed to determine if serotonin-norepinephrine reuptake inhibitors are also a viable treatment option for symptoms of social anxiety. Specifically, the study was undertaken to compare venlafaxine ER with placebo and an established treatment option (ie, paroxetine) in adult outpatients with generalized SAD.

STUDY DESIGN

This was a randomized, double-blind, placebo-controlled, parallel-group comparison of flexible doses of venlafaxine ER and paroxetine in outpatients with DSM-IV generalized SAD conducted at 26 centers in the United States. The protocol was approved by an institutional review board for each site, and patients provided written informed consent to participate. As part of the DSM-IV criteria, patients had to have a marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others, and the fears had to include at least 4 social situations. Evaluations for SAD and other Axis I diagnoses were made using the Mini-International Neuropsychiatric Interview, which was modified by replacing the social phobia module (module G) with the more rigorous social phobia module from the Mini-International Neuropsychiatric Interview–Plus.

After a 7±3-day (mean ± SD), single-blind, placebo lead-in period, eligible patients were randomly assigned to receive flexible doses of venlafaxine hydrochloride ER (75-225 mg/d), paroxetine (20-50 mg/d), or placebo for up to 12 weeks, followed by a taper period of up to 2 weeks. Starting doses were 75 mg/d for venlafaxine hydrochloride ER and 20 mg/d for paroxetine. If clinically indicated to improve response, daily doses could be titrated upward each week by 75 mg for venlafaxine hydrochloride ER or 10 mg for paroxetine to a maximum of 225 mg/d of venlafaxine hydrochloride ER and 50 mg/d of paroxetine. The dosage could be reduced at any time to improve tolerance; however, the minimum allowed dosages after day 7 were 75 mg/d for venlafaxine hydrochloride ER and 20 mg/d for paroxetine. Outpatients 18 years and older who fulfilled the DSM-IV criteria for SAD for 6 months or longer at screening were eligible to participate in the study. In addition, patients were required to have a Liebowitz Social Anxiety Scale (LSAS) score of 50 or more at prestudy and baseline, with a decrease of 30% or less between the prestudy and baseline evaluations; a score of 4 or more on the Clinical Global Impression–Severity of Illness (CGI-S) scale (item 1); a prestudy Covi Anxiety Scale total score greater than the Raskin Depression Scale total score (with a Raskin Depression Scale total score of ≤9 and scores of ≤3 on each item); and a prestudy 17-item Hamilton Psychiatric Rating Scale for Depression score of less than 15, with a score of 2 or less on the depressed mood item. Patients with a clinically important Axis I or Axis II disorder other than SAD or avoidant personality disorder were excluded, as were those with a history or current diagnosis of any psychotic illness, patients who were suicidal, and those with a history of drug or alcohol dependence (as defined in DSM-IV) within 1 year of study start. In addition, patients were ineligible if they had used any psychopharmacologic medications within 7 days before study day 1; used antidepressants (other than fluoxetine), anxiolytics, or herbal products intended to treat anxiety or depression within 14 days of the study; received electroconvulsive therapy within 6 months of the study; or used antipsychotic medication.
medications or fluoxetine or received treatment with formal psychotherapy within 30 days of the study. Patients with clinically significant abnormal findings on laboratory tests, electrocardiograms, or physical examinations; those with abnormal vital signs; those with a history or presence of clinically important medical conditions (including head trauma and seizure disorders); and women of childbearing potential who were pregnant, breastfeeding, or not using a medically acceptable form of contraception were prohibited from participating.

OUTCOMES

Safety assessments included reports of adverse events and measurements of vital signs, recorded at each visit, and routine physical examinations, laboratory determinations, and electrocardiograms, assessed at the prestudy (or baseline) visit and on the last day on which the patient took a full dose of study medication (ie, before taper).

STATISTICAL ANALYSIS

Statistical analyses were performed using last-observation-carried-forward values for the intent-to-treat population, which was defined as all patients who had taken at least 1 dose of study medication and had a baseline observation and at least 1 on-therapy observation.

The primary efficacy time point was the final on-therapy (defined as observations that occurred within 3 days of the patient’s last full dose of study medication) LSAS total score. The week 12 last-observation-carried-forward values were the final on-therapy observations. Changes from baseline scores on the LSAS total, the LSAS fear/anxiety and avoidance subscales, the Social Phobia Inventory, and the Sheehan Disability Inventory were analyzed using an analysis of covariance, with treatment and investigator as main effects and baseline score as the covariate. Changes from baseline scores on the CGI-S were analyzed using an analysis of covariance, with treatment, investigator, and baseline CGI-S score as main effects. The CGI–Improvement (CGI-I) scores were analyzed using the same model as the CGI-S scores, except that there was no baseline CGI-I to enter into the model. The primary comparison was between the venlafaxine ER–treated group and the placebo-treated group. Comparisons between the paroxetine group and the venlafaxine ER group and between the paroxetine group and the placebo group were considered secondary. The α level was set at .05, 2-sided, for all statistical tests.

RESULTS

DEMOGRAPHIC AND BASELINE CHARACTERISTICS

A total of 440 patients completed the placebo run-in period and were randomly assigned to receive venlafaxine ER (n = 146), paroxetine (n = 147), or placebo (n = 147). Of these patients, 11 failed to return after the baseline visit; thus, 429 patients were included in the safety analyses. Baseline clinical and demographic characteristics for the intent-to-treat population are shown in Table 1. There were no statistically significant differences between the treatment groups for any of the demographic or baseline characteristics.

PATIENT DISPOSITION

Of the 429 patients included in the safety population, 16 (3.7%) had no efficacy evaluation beyond baseline or no evaluation on therapy or within 3 days of the final dose of study drug and, therefore, are not included in the intent-to-treat population (n = 413). Three hundred eighteen patients (74.1%) completed the 12-week double-blind treatment period and 111 (25.9%) withdrew from the study. The reasons for discontinuation are listed in Table 2. Significantly (P = .004, Fisher exact test) more patients in the active treatment groups (venlafaxine ER and paroxetine) withdrew because of adverse events than in the placebo group, while significantly (P = .009, Fisher exact test) more patients in the placebo group withdrew because of lack of efficacy; however, there were no significant differences between the active treatment groups.

EFFICACY

Primary Efficacy Assessment

A reduction in mean LSAS total scores was significantly greater in the venlafaxine ER and paroxetine groups com-
pared with the placebo group \( (P < .05) \). Significant differences between the venlafaxine ER group and the placebo group were seen from weeks 1 through 12 \( (P < .05 \text{ for weeks 1-3}, P < .01 \text{ for weeks 4 and 6, and } P < .001 \text{ for weeks 8-12}) \), and between the paroxetine and placebo groups from weeks 3 through 12 \( (P < .05 \text{ for week 3, } P < .01 \text{ for week 4, and } P < .001 \text{ for weeks 6-12}) \) (Figure 1). At end point, the adjusted mean change from baseline was −35.00 (SE, 2.64) for venlafaxine ER, −39.20 (SE, 2.58) for paroxetine, and −22.20 (SE, 2.47) for placebo. No significant differences were noted between the venlafaxine and paroxetine groups.

Secondary Efficacy Variables

At end point, both active treatment groups demonstrated significant improvement compared with placebo on all secondary efficacy measures and no significant differences were observed between the venlafaxine ER group and the paroxetine group.

On the patient-rated Social Phobia Inventory, significantly greater improvement over placebo was observed with venlafaxine ER treatment beginning at week 1 \( (P < .01 \text{ for week 1 and } P < .001 \text{ for weeks 2-12}) \), and with paroxetine treatment beginning at week 3 \( (P < .05 \text{ for week 3, } P < .01 \text{ for week 4, and } P < .001 \text{ for weeks 6-12}) \) (Figure 2). In addition, venlafaxine-treated patients showed significantly greater improvement than paroxetine-treated patients at weeks 1 and 2 \( (P < .01 \text{ and } P < .05, \text{ respectively}) \).

For the fear/anxiety and avoidance subscales of the LSAS, patients in both active treatment groups improved to a significantly greater extent compared with patients in the placebo group: venlafaxine ER–treated patients improved beginning at week 1 and continuing through the end of treatment \( (P < .05 \text{ for weeks 1-3}, P < .01 \text{ for weeks 4 and 6, and } P < .001 \text{ for weeks 8-12}) \), and paroxetine-treated patients improved beginning at week 3 \( (P < .05 \text{ for week 3, } P < .01 \text{ for week 4, and } P < .001 \text{ for weeks 6-12}) \).

Significantly greater improvement compared with placebo-treated patients was demonstrated in venlafaxine ER–treated patients on the CGI-I at week 2 \( (P < .05) \) and weeks 6 through 12 \( (P < .01 \text{ for week 6 and } P < .001 \text{ for weeks 8-12}) \) and in paroxetine-treated patients at weeks 3 through 12 \( (P < .05 \text{ for week 3 and } P < .001 \text{ for weeks 4-12}) \). The difference in baseline to end point change vs placebo was −0.56 (95% confidence interval, −0.83 to −0.28) for the venlafaxine group and −0.73 (95% confidence interval, −1.00 to −0.45) for the paroxetine group \( (P < .001 \text{ for both groups vs placebo; no significant differences existed between active treatment groups}) \).

At end point, mean CGI-I scores showed greater improvement for the venlafaxine ER and paroxetine groups \( (2.32 \text{ and } 2.24, \text{ respectively}) \) vs the placebo group \( (2.93) \) \( (P < .001 \text{ for both}) \). Significant differences were observed with venlafaxine ER–treated patients beginning at week 4 \( (P < .05 \text{ for weeks 4 and 6 and } P < .001 \text{ for weeks 8-12}) \) and with paroxetine-treated patients beginning at week 3 \( (P < .05 \text{ for week 3 and } P < .001 \text{ for weeks 4-12}) \).

At week 12, more patients in the venlafaxine ER \( (78 \% \text{ of } 133 \text{ patients}) \) and paroxetine \( (85 \% \text{ of } 136 \text{ patients}) \) groups were considered responders (CGI-I score, 1 or 2) compared with patients in the placebo group \( (52 \% \text{ of } 144 \text{ patients}) \) \( (P < .001 \text{ for both}) \). Significant differences in response rates vs placebo were noted at week 2 and weeks 6 through 12 for the venlafaxine ER group \( (P < .05 \text{ for weeks 2 and 6 and } P < .001 \text{ for weeks 8-12}) \) and at weeks 4 through 12 for the paroxetine group \( (P < .01 \text{ for weeks 4 and 6 and } P < .001 \text{ for weeks 8-12}) \) (Figure 3).

Health Outcomes

Improvement in all domains of the Sheehan Disability Inventory (work, social life/leisure activities, and family life/home responsibilities) and Global Work and Social Dis-

Table 2. Patients Who Withdrew During the Double-blind Period by Primary Reason*

<table>
<thead>
<tr>
<th>Primary Reason</th>
<th>Placebo Group (n = 146)</th>
<th>Venlafaxine Hydrochloride ER Group (n = 141)</th>
<th>Paroxetine Group (n = 142)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any reason</td>
<td>33 (22.6)</td>
<td>38 (27.0)</td>
<td>40 (28.2)</td>
</tr>
<tr>
<td>Adverse event</td>
<td>6 (4.1)</td>
<td>20 (14.2)</td>
<td>19 (13.4)</td>
</tr>
<tr>
<td>Unsatisfactory response (efficacy)</td>
<td>8 (5.5)</td>
<td>1 (0.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Failed to return</td>
<td>8 (5.5)</td>
<td>7 (5.0)</td>
<td>11 (7.7)</td>
</tr>
<tr>
<td>Other event</td>
<td>1 (0.7)</td>
<td>3 (2.1)</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>Patient request unrelated to study</td>
<td>3 (2.1)</td>
<td>1 (0.7)</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>Protocol violation</td>
<td>7 (4.8)</td>
<td>6 (4.3)</td>
<td>5 (3.5)</td>
</tr>
</tbody>
</table>

Abbreviation: See Table 1.

*Data are given as number (percentage) of each group.
Paroxetine vs Placebo.

Disability (both active treatment groups in Global Work and Social life/leisure activities (P main effects. The asterisk indicates analysis of covariance was performed, with treatment and investigator as main effects and baseline score as the covariate. The asterisk indicates .05 for paroxetine vs placebo; double dagger, .001 for venlafaxine ER vs paroxetine.

Both active treatments were relatively well tolerated. Treatment-emergent adverse events were reported for 85.6% (125/146) of the placebo group, 95.7% (135/141) of the venlafaxine ER group, and 91.5% (130/142) of the paroxetine group. The most commonly reported treatment-emergent adverse events (incidence ≥10% and at least twice that of placebo) are listed in Table 3. The mean±SD daily doses of venlafaxine ER and paroxetine at week 12 were 201.7±38.1 and 46.0±7.9 mg, respectively. Twenty patients (13.7%) in the venlafaxine ER group, 19.2 (12.9%) in the paroxetine group, and 6 (4.1%) in the placebo group discontinued therapy because of adverse events as the primary reason for withdrawal (P = .05 for both active treatments vs placebo). Doses were reduced because of adverse events in 23 (15.8%) venlafaxine ER–treated patients (P < .001 vs placebo and P < .05 vs paroxetine), 11 (7.5%) paroxetine-treated patients (P = .22 vs placebo), and 6 (4.1%) placebo-treated patients.

Clinically important changes in laboratory test results were observed in 14 patients (8 in the placebo group, 3 in the venlafaxine ER group, and 3 in the paroxetine group). These abnormalities included increased triglycerides, total cholesterol, low-density lipoprotein cholesterol, and uric acid levels and a decreased high-density lipoprotein cholesterol level. In addition, small but statistically significant mean increases in total cholesterol were observed for the venlafaxine ER (7.73 mg/dL | 0.20 mmol/L).

Table 3. Most Commonly Reported Treatment-Emergent Adverse Events (Incidence ≥10% and at Least Twice That of Placebo)*

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo Group (n = 146)</th>
<th>Venlafaxine Hydrochloride ER Group (n = 141)</th>
<th>Paroxetine Group (n = 142)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>16 (11.0)</td>
<td>46 (32.6)</td>
<td>37 (26.1)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>12 (8.2)</td>
<td>39 (27.7)</td>
<td>26 (18.3)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>13 (9.0)</td>
<td>38 (27.0)</td>
<td>38 (26.8)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>15 (10.3)</td>
<td>29 (20.6)</td>
<td>34 (23.9)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>7 (4.8)</td>
<td>25 (17.7)</td>
<td>23 (16.2)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>5 (3.4)</td>
<td>20 (14.2)</td>
<td>15 (10.6)</td>
</tr>
<tr>
<td>Yawn</td>
<td>0</td>
<td>19 (13.5)</td>
<td>10 (7.0)</td>
</tr>
<tr>
<td>Libido decreased</td>
<td>7 (4.8)</td>
<td>15 (10.6)</td>
<td>18 (12.7)</td>
</tr>
<tr>
<td>Abnormal ejaculation/ orgasm (men)†</td>
<td>0</td>
<td>8 (5.0)</td>
<td>16 (20.8)</td>
</tr>
<tr>
<td>Constipation</td>
<td>6 (4.1)</td>
<td>16 (11.3)</td>
<td>11 (7.7)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>6 (4.1)</td>
<td>14 (9.9)</td>
<td>3 (2.1)</td>
</tr>
<tr>
<td>Sweating</td>
<td>5 (3.4)</td>
<td>14 (9.9)</td>
<td>11 (7.7)</td>
</tr>
</tbody>
</table>

Abbreviation: See Table 1.
*Data are given as number (percentage) of each group.
†Data are based on the number of men: placebo group, n = 76; venlafaxine ER group, n = 73; and paroxetine group, n = 77.
mmol/L; \( P < .01 \) and paroxetine (5.80 mg/dL [0.15 mmol/L]; \( P < .05 \)) groups. These increases were significantly different from the decrease observed in the placebo group (−3.87 mg/dL [−0.10 mmol/L]) (\( P \leq .05 \) for both). Finally, small mean increases in high-density lipoprotein cholesterol reported in the venlafaxine ER and paroxetine groups (1.16 mg/dL [0.03 mmol/L] and 1.55 mg/dL [0.04 mmol/L], respectively) were significantly different compared with the placebo group (−1.16 mg/dL [−0.03 mmol/L]) (\( P \leq .05 \) for both) at week 12.

At the final on-therapy evaluation, mean changes from baseline in supine diastolic blood pressure were −1.26 mm Hg for the placebo group (\( P < .01 \) vs the baseline mean), 1.05 mm Hg for the venlafaxine ER group (\( P < .01 \) vs the baseline mean), and 0.35 mm Hg for the paroxetine group (\( P = \text{not significant vs the baseline mean} \)). The increases in diastolic blood pressure associated with venlafaxine ER and paroxetine were significantly different from the decrease associated with placebo (\( P < .05 \) for both). Treatment-related changes in diastolic blood pressure were not significantly different between the venlafaxine ER and paroxetine groups.

Changes from baseline in mean supine systolic blood pressure were −1.86 mm Hg for placebo-treated patients (\( P < .001 \) vs the baseline mean), 1.00 mm Hg for venlafaxine ER–treated patients, and 0.87 mm Hg for paroxetine-treated patients at the final on-therapy evaluation. The mean increases in systolic blood pressure associated with venlafaxine ER and paroxetine treatment were not significantly different from the respective baseline means, but were both significantly different from the decrease associated with placebo (\( P < .05 \)). Differences between changes associated with venlafaxine ER and paroxetine treatment were not significant.

Mean weight changes were 0.42, −1.23, and 0.21 kg for the placebo, venlafaxine ER, and paroxetine groups, respectively, at the final on-therapy evaluation. The decrease in mean body weight in the venlafaxine ER group was significantly different from the increase with placebo and paroxetine at week 12 and at the final on-therapy evaluation.

Changes of clinical importance in vital signs and weight occurred in 6 patients. One placebo-treated patient experienced an elevated standing diastolic blood pressure (increase of ≥15 mm Hg and pressure of ≥105 mm Hg), 1 venlafaxine ER–treated patient had hypertension (systolic blood pressure increase ≥20 mm Hg and pressure of ≥180 mm Hg and diastolic blood pressure increase ≥15 mm Hg and pressure of ≥105 mm Hg), 1 paroxetine-treated patient had an increased diastolic blood pressure, 1 paroxetine-treated patient had orthostatic hypotension, and 2 paroxetine-treated patients had significant weight gain (increase of ≥7% in body weight). Clinically significant changes in electrocardiographic results were reported only for 2 placebo-treated patients.

**COMMENT**

To our knowledge, this study is one of the largest comparative studies of pharmacotherapeutic treatment options for generalized SAD. Previous comparative studies of pharmacotherapeutic treatment options for generalized SAD. Previous comparative studies

(Reprinted) Arch Gen Psychiatry/Vol. 62, Feb 2005 www.archgenpsychiatry.com

©2005 American Medical Association. All rights reserved.
ductions due to adverse events were more common among venlafaxine ER–treated patients than paroxetine–treated patients, discontinuations due to adverse events were similar between the 2 groups. While mean effects on cholesterol and lipoprotein levels were small for both active drugs, clinically these should be monitored in patients considered high risk because of preexisting health issues. The small but significant weight loss seen with venlafaxine may also be desirable for some patients.

Given that some practitioners are reluctant to use venlafaxine ER as a first-line agent for patients with symptoms of anxiety because of the fear that in the early treatment phase it may cause agitation or exacerbate such symptoms, it is important to note that venlafaxine ER treatment was not associated with a significantly greater incidence of agitation or nervousness compared with paroxetine or placebo treatment in this study. Rather, the results are indicative of the agent’s substantial anxiolytic properties in patients with SAD.

The results of this trial are consistent with those of trials with other antidepressants for the treatment of generalized SAD and are similar to data from other trials of venlafaxine ER in those with SAD.66,67 The performance of paroxetine is consistent with the results of previously published studies of paroxetine.30-33,35-38 The consistency across studies is typical of clinical research in this patient population. In contrast to more heterogeneous populations (eg, the clinically diverse spectrum of depressed patients), there is considerably less variability among patients with generalized SAD. The wide variation in results observed in studies of antidepressants in the treatment of depressed patients is uncommon in studies of generalized SAD, which lends confidence to the reliability and reproducibility of the results of individual studies.

One limitation of the present study is the 12-week duration. The early onset, chronic nature, and duration of illness associated with SAD render it a difficult illness to treat; full response to treatment may take longer than 12 weeks. In addition, although synaptic levels of neurotransmitters change relatively quickly in response to treatment, this is believed to be only a first step in a process leading to receptor adaptation, which takes longer to occur. Thus, the results of the study may not reflect the full efficacy potential of the active agents. Consistent with this construct, there was a trend for increased improvement over time, suggesting that a longer study period might continue to yield increasingly higher response rates. Further improvement was also noted in SAD patients taking sertraline over the 24 weeks of a maintenance phase following a 20-week short-term trial.68

An additional limitation of the study was the exclusion of patients with comorbid psychiatric disorders. Given the high rate of comorbidity observed in this population, the study group may not have included the most common patient type seen in clinical practice. In contrast to depressive disorders, however, the presence of comorbidities in patients with SAD generally does not significantly affect response to treatment.69 Hence, despite this exclusion criterion, the results remain relatively generalizable to clinical practice.

In conclusion, in this study of adult outpatients, venlafaxine ER had an efficacy and tolerability profile comparable to that of paroxetine in the short-term treatment of generalized SAD. Thus, in addition to its established efficacy in the treatment of depression and generalized anxiety disorder, the results indicate that venlafaxine ER is a viable first-line treatment option for patients with generalized SAD.

Submitted for Publication: October 14, 2003; final revision received June 16, 2004; accepted August 19, 2004.

Author Affiliations: New York State Psychiatric Institute, New York (Dr Liebowitz); Arizona Health Services Center, Tucson (Dr Gelenberg); and Southwestern Research Institute, Beverly Hills, Calif (Dr Munjack).

Financial Disclosure: Dr Liebowitz consults for or is on the scientific advisory board of Wyeth-Ayerst, Bristol-Myers Squibb, GlaxoSmithKline, Pfizer Inc, Novartis, Forest, Eli Lilly and Company, and UCB Pharma; receives honoraria for speaking at GlaxoSmithKline Beecham, Pfizer Inc, Pharmacia, Wyeth-Ayerst, and Novartis; and performs research for Eli Lilly and Company, Novartis, GlaxoSmithKline, Pfizer Inc, Forest, Phener Pharmaceuticals, Inc, Wyeth-Ayerst, UCB Pharma, and Cephalon, Inc. Dr Gelenberg receives grant/research support from Pfizer Inc and Wyeth; consults for Eli Lilly and Company, Pfizer Inc, Vela Pharmaceuticals Inc, Best Practice, Bristol-Myers Squibb, AstraZeneca, Wyeth, GlaxoSmithKline, Cyberonics, UCB Pharma, Roche, and ZARS, Inc; and is on the speakers’ bureau at Wyeth and Pfizer Inc.

Correspondence: Michael R. Liebowitz, MD, New York State Psychiatric Institute, 1051 Riverside Dr, Unit 120, New York, NY 10032 (mrl1945@aol.com).

Investigators: The investigators for the study were as follows: M. Bloch, MD, Affiliated Research Institute Berkeley, Berkeley, Calif; R. Burch, MD, University of Missouri-Columbia; C. Cornelius, MD, Samaritan Behavioral Health Center, Good Samaritan Regional Medical Center, Phoenix, Ariz; N. DeMartinis, MD, Department of Psychiatry, Neuropsychological Treatment, Research, and Training Center, University of Connecticut Health Center, Farmington; M. DePriest, MD, Las Vegas Center for Clinical Research, Las Vegas, Nev; H. De Silva, MD, Affiliated Research Institute, Santa Ana, Calif; M. Drehoeb, MD, Scripps Clinic, San Diego, Calif; J. Fahs, MD, IATRX, Inc, Cary, NC; J. Ferguson, MD, Pharmacology Research Clinic, Salt Lake City, Utah; A. Gelenberg, MD, Department of Psychiatry, Arizona Health Services Center, Tucson; R. Gopalan, MD, ICSL–Clinical Studies, Falls Church, Va; J. Hartford, MD, Hartford Research Group, Florence, Ky; J. Hartford, MD, Summit Research Network (Ohio) LLC, Cincinnati; R. Hayward, MD, Department of Psychiatry, Stanford University, Stanford, Calif; C. Hemlock, MD, Radiant Research Austin, Austin, Tex; L. Kirby, MD, Pivotal Research Centers, Peoria, Ariz; R. Levine, MD, Department of Psychiatry and Behavioral Sciences, University of Texas Medical Branch, Galveston; M. Liebowitz, MD, The Medical Research Network, LLC, New York, NY; D. Munjack, MD, Southwestern Research Institute, Beverly Hills, Calif; A. Poidexter III, MD, Advances in Health, Houston, Tex; R. Rivas-Vazquez, MD, Miami Research Associates, Miami, Fla; J. Ross, MD, Chicago Center for Clinical Research, Chi-

(RePRINTed) ARCH GEN PSYCHIATRY/VOL 62, FEB 2005 WWW.ARCHGENPSYCHIATRY.COM

©2005 American Medical Association. All rights reserved.
REFERENCES


