A Randomized, Placebo-Controlled, Dose-Response Trial of Venlafaxine Hydrochloride in the Treatment of Major Depression

Richard L. Rudolph, M.D., Louis F. Fabre, M.D., Ph.D., John P. Feighner, M.D., Karl Rickels, M.D., Richard Entsuah, Ph.D., and Albert T. Derivan, M.D.

Background: We examined the efficacy and safety of three different dosages of venlafaxine hydrochloride (75, 225, and 375 mg/day) in a multicenter, randomized, double-blind, placebo-controlled, four-group study.

Method: Outpatients, 18 to 65 years old, who met DSM-III criteria for major depression were included (N = 358 randomized; 194 completed). Of the total patients completing the trial, 59%, 56%, 51%, and 51% were in the placebo, 75-mg, 225-mg, and 375-mg groups, respectively. The primary outcome measures were the Hamilton Rating Scale for Depression (HAM-D_{21}) total, HAM-D_{21} depression item, Montgomery-Asberg Depression Rating Scale total, and Clinical Global Impressions scale.

Results: Each dosage of venlafaxine was associated with statistically significant improvement as compared with placebo, based on the intent-to-treat sample. The two higher dosages were associated with a modestly greater antidepressant response than was the 75-mg dosage. Nausea, dizziness, somnolence, and anorexia were the most common adverse events attributable to venlafaxine. Since headache occurred at a similar frequency in both the drug and placebo groups, we did not consider it to be attributable to venlafaxine use. Withdrawal from the study due to adverse events occurred in 5%, 17%, 24%, and 30% of the patients in the placebo, 75-mg, 225-mg, and 375-mg groups, respectively.

Conclusion: Venlafaxine, at dosages of 75–375 mg/day, is an effective and well-tolerated antidepressant. With increasing dosage, greater efficacy and possibly more adverse effects will occur.

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Reprint requests to: Richard L. Rudolph, M.D., Clinical Research and Development, Wyeth-Ayerst Research, P.O. Box 8299, Philadelphia, PA 19101.

Venlafaxine hydrochloride (hereafter referred to as venlafaxine) is among the newer antidepressant drugs. It possesses a relatively unique pharmacologic profile; it inhibits the neuronal uptake of serotonin, norepinephrine, and, to a small extent, dopamine, but it has no monoamine oxidase (MAO)–inhibitory activity. Venlafaxine lacks affinity for muscarinic cholinergic, histaminergic, and adrenergic receptors in the brain of rats.[1] Unlike currently available antidepressant drugs, it produces a rapid decrease in β-adrenergic responsiveness in the rat pineal cyclic adenosine monophosphate (cAMP) model (data on file, Wyeth-Ayerst Research). Earlier results from preliminary uncontrolled, open-label trials in humans[2,3] and the published results from specific sites of this trial, including 153 of the patients evaluated in this study,[4,5] had suggested that venlafaxine has antidepressant activity and is well tolerated.

We report here the complete results of our placebo-controlled trial of venlafaxine. The objective was to compare the acute phase antidepressant efficacy and short-term tolerability and safety of three different dosages of venlafaxine with those of placebo.

METHOD

Design

Our study used a double-blind, parallel-group design in which patients were randomized in blocks of eight using a table of random numbers. Patients who met the enrollment criteria (below) were randomly assigned to one of the four treatment groups: venlafaxine 75 mg/day, venlafaxine 225 mg/day, venlafaxine 375 mg/day, or placebo. We conducted the trial at multiple outpatient psychiatric clinics and private psychiatric practices.

Study Population

The study population consisted of psychiatric outpatients between the ages of 18 and 65 who met *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-*III* criteria for major depression.[6] In addition, symptoms of depression had to have been present for at least 1 month before study entry, and the patients had to have minimum prestudy and baseline (after washout) scores of 20 on the 21-item Hamilton Rating Scale for Depression ($HAM\text{-}D_{21}$).[7] Subjects were recruited by advertisement and physician referral. Inclusion and exclusion criteria were the same as those described in preliminary reports from this study[4,5]: i.e., subjects were outpatients who required a diagnosis of major depression as determined in DSM-III and had a total score ≥ 20 on the $HAM\text{-}D_{21}$. Women of childbearing age were not recruited, nor were subjects with bipolar mood disorder (or bipolar II), schizophrenia, and other psychotic disorders. There were no inclusion/exclusion criteria pertaining to baseline systolic or diastolic blood pressure values or history of treatment resistance. After candidates were fully informed about study procedures, each patient gave written consent to participate.

Drug Treatment

A 4- to 7-day washout period with placebo preceded the study; the protocol specified longer washout periods for certain classes of medication (investigational drugs, antipsychotic drugs, and thyroid-hormone preparations, 30 days; all antidepressants, 14 days). The double-blind treatment phase followed, and medication was administered three times daily for up to 45 days. Patients in the two highest venlafaxine dosage groups (225 and 375 mg) were given lower dosages for the first 7 days (75–150 mg and 150–225 mg, respectively) and the last 3 days (150 and 225 mg, respectively) of the trial. Tapering of the drug regimens was included in the protocol to avoid adverse effects (i.e., nausea, dizziness, headaches) common with the abrupt discontinuation of many antidepressant drugs.

After stabilization of the randomized dose of study medication (Days 8 to 42), the dosage could be reduced once, if necessary, by 75 mg/day to improve the patients' tolerance for the study medication. As a result, patients in the 375-mg dosage group could have actually received 300 or 375 mg/day, and patients in the 225-mg dosage group could have received 150 or 225 mg/day. Dosages were not reduced for the patients in the 75-mg dosage group.

Concomitant treatment with any psychopharmacologic drugs or other drugs and substances that have psychotropic effects—other than the test medication and chloral hydrate for sleep—was not allowed during the trial. Psychotherapy was also prohibited during the trial.

Assessments

Antidepressant efficacy was assessed with standard scales for measuring depression just before the initial administration of study drug and at the end of Weeks 1, 2, 3, 4, and 6. The $HAM\text{-}D_{21}$ total score, the $HAM\text{-}D_{21}$ depression item score, the Montgomery-Asberg Depression Rating Scale (MADRS) total score,[8] and the Clinical Global Impressions (CGI) scale scores were identified as the primary efficacy variables before the data were unblinded and analyzed. Between-rater reliability for the primary efficacy variables was established through the use of videotaped interviews with depressed patients.

Safety was assessed at regular intervals throughout the trial by physical examinations, measurement of vital signs, laboratory determinations, electrocardiograms, and recording of adverse events.

Data Analyses

We analyzed efficacy data on the basis of the intent-to-treat subset of the total number of patients enrolled. This subset consisted of all patients who had been randomly assigned to receive double-blind treatment, received at least one dose, and had had at least one efficacy evaluation during the treatment period or within 3 days of the last dose of study medication. The data from the intent-to-treat patients were analyzed using an observed-cases analysis, which included all data available at each evaluation time. The final evaluation is like the last-observation-carried-forward (LOCF) analysis, in which the last observation for patients who withdrew before the scheduled study completion is carried forward into all subsequent time periods.

Response rates were calculated for each treatment group on the basis of the $HAM\text{-}D_{21}$ and MADRS total scores and the CGI-Improvement (CGI-I) item. Response on the $HAM\text{-}D_{21}$ and MADRS scales was defined as a 50% or more decrease from baseline; response on the CGI-I scale was defined as a score of 1 (very much improved) or 2 (much improved).

Statistical analyses were conducted on pooled data from the individual study sites. All tests of hypotheses were two-sided. Results of statistical analyses were considered to be significant when the p value was $\leq .05$. Analysis of variance (ANOVA) was used to test for com-

Table 1. Demographic Data

Characteristic	Placebo (N = 92)	Venlafaxine 75 mg (N = 77)	Venlafaxine 225 mg (N = 79)	Venlafaxine 375 mg (N = 75)
Age (y)				
Mean	41.5	43.6	43.1	43.8
Range	19–64	22–64	21–65	23–64
SD	11.27	10.91	9.61	10.33
Median	40	42	42.5	45
Sex, N (%)				
Male	63 (68%)	46 (60%)	45 (57%)	50 (67%)
Female	29 (32%)	31 (40%)	34 (43%)	25 (33%)
Duration of current episode (wk)				
Mean	93.7	108.3	119.3	113.4
SD	168.9	233.6	195.5	207.9
Median	26	40	50	41
Race, N (%)				
White	79 (86%)	69 (90%)	63 (80%)	64 (85%)
Black	6 (6%)	4 (5%)	13 (16%)	5 (7%)
Other	7 (8%)	4 (5%)	3 (4%)	6 (8%)

parability of the treatment groups with respect to factors such as demographic characteristics.

The chi-square (χ^2) test was used to analyze categorical data. These included some demographic characteristics (race, sex, presence of precipitating factors, duration of current depressive episode), the percentage of patients who withdrew, the incidence of adverse events, and response rates. Pairwise comparisons were done with Fisher's exact test for those variables whose group comparisons were statistically significantly different.

Scores on the efficacy scales were analyzed using a two-way analysis of covariance (ANCOVA) with treatment and investigator as factors. The dosage relationship in the efficacy data was analyzed using the Jonckheere-Terpstra test for ordered alternatives.[9] Laboratory data, weight, vital signs, and electrocardiogram results were analyzed over time and by treatment group using the paired t test and ANCOVA, respectively. For the continuous variables, the multiple comparison procedure used was the least significant difference method.

RESULTS

In total, 358 patients were randomly assigned to receive study medication under double-blind conditions and provided evaluable safety information. Of these patients, 35 were excluded from the intent-to-treat analysis because they did not have an efficacy rating during the treatment period or within 3 days of their last dose of study medication. Thus, 323 patients were included in the intent-to-treat analysis (Table 1).

No statistically significant differences were found between the four treatment groups in the intent-to-treat subset for mean age ($F = 0.80$, $df = 3$, $p = .493$), sex distribution ($\chi^2 = 3.21$, $df = 3$, $p = .361$), or racial distribution ($\chi^2 = 9.44$, $df = 3$, $p = .150$). There was also no difference in the distribution for the duration of the current episode of depression ($\chi^2 = 17.07$, $df = 15$, $p = .315$). Mean baseline HAM-D_{21} ($F = 1.67$, $df = 3$, $p = .174$) and MADRS total scores ($F = 0.83$, $df = 3$, $p = .479$) were also similar in the four groups.

Patients who completed the trial totaled 194, including 59% from the placebo group and 56%, 51%, and 51% from the 75-mg, 225-mg, and 375-mg venlafaxine treatment groups, respectively. Adverse events were the most common primary reasons for the withdrawal of patients treated with venlafaxine—15 (17%), 21 (24%), and 26 (30%) patients in the 75-mg, 225-mg, and 375-mg venlafaxine groups, respectively, and 5 (5%) patients in the placebo group ($\chi^2 = 1.70$, $df = 3$, $p = .638$). Most of the withdrawals related to adverse events occurred within the first 2 weeks. Failure to return and unsatisfactory response were the most common primary reasons for discontinuation or withdrawal among patients given placebo. Unsatisfactory response was given as a reason by 15% of the patients in the placebo group and by 5%–7% of the patients in the venlafaxine groups.

Mean daily dosages of study medication for each treatment group were calculated on the basis of dosing information collected from the patients by the investigators. Compliance was verified by pill counts. After initial titration, the mean daily dosage ranged from 71 to 72 mg in the 75-mg dosage group, from 194 to 211 mg in the 225-mg dosage group, and from 322 to 356 mg in the 375-mg dosage group.

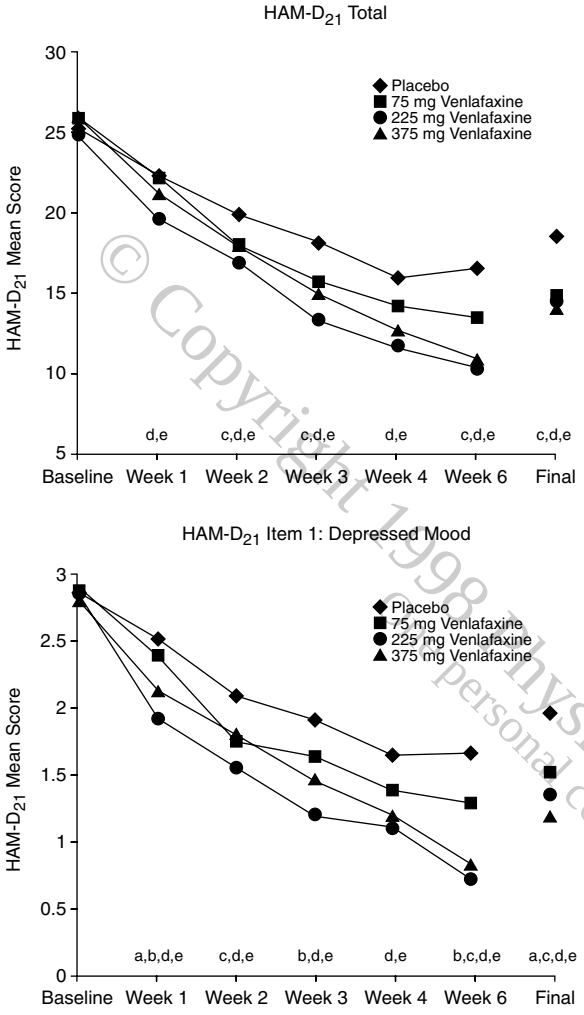
Efficacy

Decreases on the HAM-D_{21} total and HAM-D_{21} depression item scores, indicative of improvement in depression, occurred in all treatment groups, but the decreases were larger in each venlafaxine group than they were in the placebo group. For each venlafaxine group, the differences from placebo at Week 6 and at the final evaluation were statistically significant. Statistically significant differences in results between the placebo group and the venlafaxine groups, especially the 375-mg dosage group, were found as early as the end of Week 1 (Figure 1).

The decreases in the MADRS total score at Week 1 were 3.1 in the placebo group and 3.9, 5.0, and 6.6 in the 75-mg, 225-mg, and 375-mg venlafaxine groups, respectively. The differences between the decreases in the 375-mg group and the placebo and 75-mg groups were statistically significant ($p = .003$ and $p = .005$, respectively). The decreases in the MADRS total scores at Week 6 were 9.0 for the placebo group and 14.4, 17.3, and 18.7 for the 75-mg, 225-mg, and 375-mg venlafaxine groups, respectively ($p \leq .05$ for the comparisons between the placebo and the 75-mg, 225-mg, and 375-mg groups and between the 75-mg and 375-mg groups).

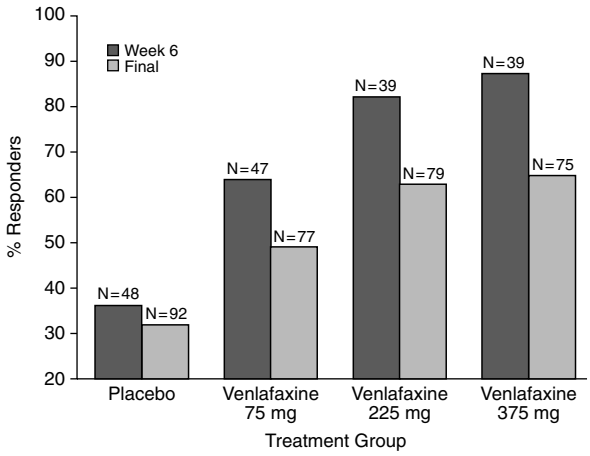
At Week 6, the CGI-Severity (CGI-S) scores decreased by 0.83 in the placebo group and 1.30, 1.87, and 1.87 in

Figure 1. Changes From Baseline Through Week 6 on HAM-D_{21} Total and HAM-D_{21} Depressed Mood Item*



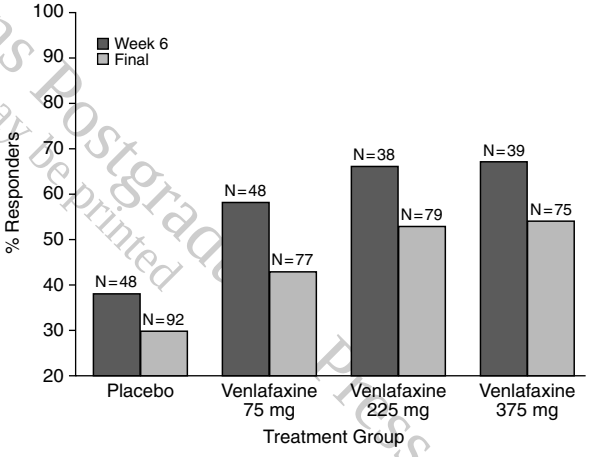
*Significant ($p \leq .05$) differences from baseline means are indicated by letters: a = 75 vs 225; b = 75 vs 375; c = 75 vs placebo; d = 225 vs placebo; e = 375 vs placebo.

Figure 2. Response Rate for Intent-to-Treat Patients on the CGI-Improvement Scale at the Week-6 and Final (LOCF) Evaluations*



*The percentage of responders was calculated as the number of responders/the number of patients evaluated × 100. The percentage of responders in each of the 75-mg, 225-mg, and 375-mg venlafaxine groups was greater (by pairwise comparisons with Fisher's exact test) than that in the placebo group for both the Week-6 ($p = .008$; $p < .001$; and $p = .008$, respectively) and the final evaluations ($p = .027$; $p < .0001$; and $p < .0001$, respectively).

Figure 3. Response Rate for Intent-to-Treat Patients on the HAM-D_{21} Scale at the Week-6 and Final (LOCF) Evaluations*



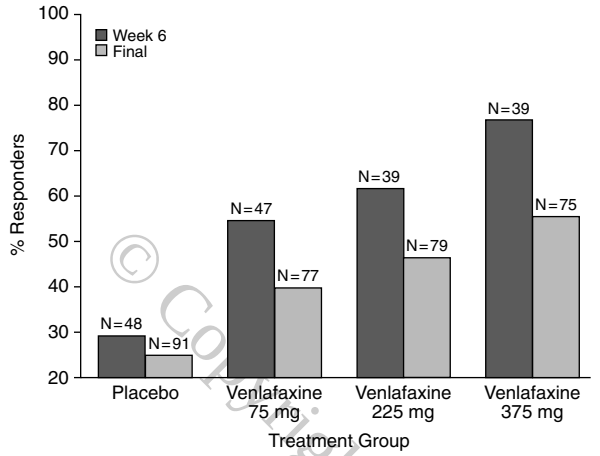
*The percentage of responders was calculated as the number of responders/the number of patients evaluated × 100. The percentage of responders in only the 225-mg and 375-mg venlafaxine groups was greater (by pairwise comparisons with Fisher's exact test) than that in the placebo group for both the Week-6 ($p < .05$; $p < .05$, respectively) and the final evaluations ($p < .05$; $p < .05$, respectively).

the 75-mg, 225-mg, and 375-mg venlafaxine groups, respectively. More improvement was observed in the 225-mg and 375-mg venlafaxine groups than in the 75-mg venlafaxine group. The differences between the two higher dosage groups and the 75-mg group were statistically significant ($p = .028$ and $p = .0031$, respectively). The differences between the two higher dosage groups and the placebo group were also statistically significant ($p \leq .05$).

Figure 2 shows the response rate on the CGI-I scale for the Week-6 and final (LOCF) evaluations. The percentages of responders in all of the venlafaxine groups were greater than those in the placebo group for both Week-6 and final evaluations. We found similar results when response was defined as a 50% or greater decrease from baseline in the HAM-D_{21} or MADRS total scores (Figures 3 and 4).

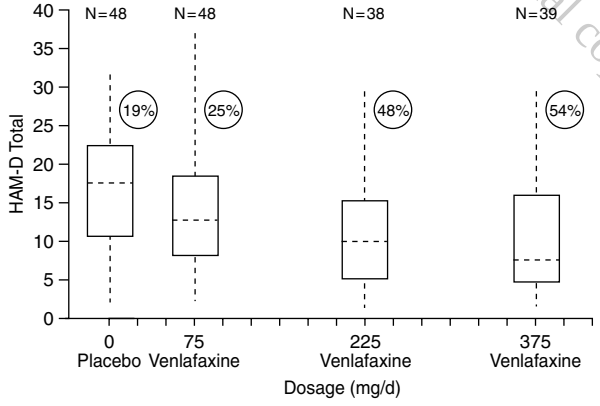
In general, the greater the venlafaxine dosage, the greater the improvement in depression scores. For example, Figure 5 illustrates the positive dose-response relationship observed at Week 6 of therapy for the HAM-D_{21} total score. We used the Jonckheere-Terpstra test for ordered alternatives to confirm this positive dose-response relationship ($p \leq .01$).

Figure 4. Response Rate for Intent-to-Treat Patients on the MADRS at the Week-6 and Final (LOCF) Evaluations*



*The percentage of responders was calculated as the number of responders/the number of patients evaluated × 100. The percentage of responders in each of the 75-mg, 225-mg, and 375-mg venlafaxine groups was greater (by pairwise comparisons with Fisher's exact test) than that in the placebo group for both the Week-6 ($p < .05$; $p < .05$; $p < .05$, respectively) and the final evaluations ($p < .05$; $p < .05$; $p < .05$, respectively).

Figure 5. Dose-Response Relationship Between Venlafaxine and HAM-D_{21} Total Score at Week 6*



*The median HAM-D_{21} total score decreased as the total daily dose of venlafaxine increased, whereas the percentage of patients who achieved a score of ≤ 8 on the HAM-D_{21} total increased as the total daily dose of venlafaxine increased. The dose-response relationship was significant ($p \leq .01$) using the Jonckheere-Terpstra test for ordered alternatives. Dotted lines indicate the full ranges of patients' scores; boxes indicate the middle 50% of patients' scores; dashed lines inside the boxes indicate the median score for the entire group; circled numbers equal the percentages of patients who achieved scores of ≤ 8 on HAM-D_{21} total.

Table 2. Treatment-Emergent Adverse Events

	Placebo (N = 92)		Venlafaxine 75 mg (N = 89)		Venlafaxine 225 mg (N = 89)		Venlafaxine 375 mg (N = 88)		
Adverse Event	N	%	N	%	N	%	N	%	Comparisons*
Anorexia	2	2	13	14	12	13	15	17	b,d,e
Constipation	10	11	17	19	10	11	17	19	…
Dizziness	4	4	17	19	20	22	21	24	b,d,e
Dry mouth	12	13	16	18	19	21	17	19	…
Headache	22	24	23	26	23	26	22	25	…
Insomnia	9	10	20	22	18	20	12	14	b
Nausea	13	14	29	32	34	38	51	58	a,b,c,d,e
Nervousness	4	4	19	21	12	13	11	13	b
Somnolence	4	4	15	17	16	18	23	26	b,d,e

*Significant ($p \leq .05$) difference between groups in pairwise comparisons by Fisher's exact test: a = 75 mg vs 375 mg; b = 75 mg vs placebo; c = 225 mg vs 375 mg; d = 225 mg vs placebo; e = 375 mg vs placebo.

Safety

Table 2 shows the treatment-emergent adverse events most commonly reported during the trial. Among venlafaxine-treated patients, nausea, dizziness, somnolence, and anorexia were the most common adverse events that did not occur at a comparable frequency among patients given placebo. Of these events, nausea was the most prevalent, showing a statistically significant relationship between the incidence of nausea and increasing doses of venlafaxine. Among patients given venlafaxine, most incidences of nausea were mild or moderate and were most commonly reported during the initial week of therapy. The prevalence of nausea among venlafaxine patients declined rapidly after the first week, even with continued administration of venlafaxine. Anticholinergic symptoms appear to have been uncommon among patients receiving venlafaxine.

Venlafaxine appears to have been generally well tolerated. The majority of patients who discontinued because of adverse events did so within the first week of the study. The most frequent adverse events cited as reasons for discontinuation of treatment by venlafaxine patients were nausea, dizziness, insomnia, and nervousness.

No clinically significant effects of venlafaxine on laboratory test results were noted, nor were there any clinically significant changes in cardiac rhythm, PR interval, QRS interval, or QT_c interval on the electrocardiographic tracings of patients given venlafaxine. However, the patients showed changes in weight and vital signs measurements.

Mean weight decreased in a dose-related manner among patients given venlafaxine. At Week 6, weight decreased by 0.2, 2.1, and 3.0 lb in the 75-mg, 225-mg, and 375-mg venlafaxine groups, respectively, whereas weight increased by 0.4 lb in the placebo group.

Mean supine pulse rate and mean supine systolic and diastolic blood pressure readings increased over time, particularly in the 375-mg venlafaxine group. At Week 6, the mean supine pulse rate in the 375-mg venlafaxine group had increased 7.7 beats per minute from baseline. Mean supine systolic and diastolic blood pressures increased by 7.3 and 7.2 mm Hg, respectively. In contrast, the mean changes in supine pulse rate for the placebo, 75-mg, and 225-mg venlafaxine groups were –1.6, 3.2, and 1.6 beats per minute, respectively. The mean changes in

systolic and diastolic blood pressure readings for the placebo, 75-mg, and 225-mg venlafaxine groups were –1.9/–2.2, –2.9/–0.1, and 1.8/0.1 mm Hg, respectively.

The increases in mean supine pulse rate and mean supine diastolic blood pressure in the 375-mg venlafaxine group were greater than those in the other two treatment groups ($F = 7.044$, $p \leq .01$, and $F = 9.198$, $p \leq .001$, respectively) and in the placebo group. The change in the mean supine systolic blood pressure in the 375-mg venlafaxine group was greater than that of the placebo and 75-mg venlafaxine groups ($F = 5.546$, $p \leq .05$). Most of the increases in blood pressure that were observed in individual patients given venlafaxine were transient. Only a few patients had clinically significant sustained increases in blood pressure readings: four patients (three in the 375-mg venlafaxine group and one in the placebo group) with baseline supine diastolic blood pressure readings of ≤ 90 mm Hg had repeated readings of ≥ 95 mm Hg during the study.

DISCUSSION

This study was the first placebo-controlled trial of the new antidepressant drug venlafaxine. We compared several different dosages of venlafaxine with placebo to examine efficacy, safety, and dose relationships before embarking on phase 3 comparative trials. The results provided clear evidence of venlafaxine's efficacy in the patients treated. Each dosage studied was associated with statistically significantly greater improvement than was placebo for each of the four predetermined primary efficacy variables. We also found a relationship between increasing dosage and increasing efficacy.

The robust improvement observed on the HAM-D_{21} depression item for the venlafaxine patients as compared with the placebo patients is consistent with a potent pharmacologic action directed against the core mood disturbance of depression and not just relief of the somatic symptoms associated with the depressive syndrome. The finding that statistically significant improvement in depression occurred after 1 week of treatment in the 375-mg venlafaxine group, relative to the improvement with placebo, is intriguing.

Venlafaxine is a potent inhibitor of the neuronal uptake of both serotonin and norepinephrine. Furthermore, among currently available antidepressants, venlafaxine appears to be unique in its ability to rapidly decrease β-adrenergic responsiveness in the rat pineal paradigm (data on file, Wyeth-Ayerst Research). These characteristics have been postulated to correlate with the speed of onset of antidepressant activity.[10] Additional studies must be done to confirm that the early onset of antidepressant activity we observed in this trial is clinically relevant.

Venlafaxine was well tolerated, especially when one considers that dose-response study designs, such as the one we used, do not permit investigators to prescribe study medications optimally in terms of a medication's tolerability. Nausea, which was often transient, was the adverse event most commonly associated with venlafaxine administration. Anticholinergic effects were uncommon.

Venlafaxine administration was associated with a slight weight loss that was dosage related. Mean systolic and diastolic blood pressures and pulse rates increased slightly in the 375-mg venlafaxine group in an apparent time-dependent manner, but we noted few instances of clinically significant sustained blood pressure elevations.

The incidence of nausea, the overall occurrence of adverse events, and the rate of study discontinuations because of adverse events all increased with increasing dosage. These findings might be attributed to differences in the titration schedules rather than to differences in the total dosage. On the other hand, the blood pressure elevation in the 375-mg dose group cannot be attributed to the more rapid titration schedule in that group, because the full expression of the phenomenon did not occur until later in the trial, after stabilization on the randomized dose of study medication.

SUMMARY AND CONCLUSION

In summary, this initial placebo-controlled trial of venlafaxine provided clear evidence of its antidepressant efficacy and demonstrated that venlafaxine is well tolerated during acute therapy. Statistically significant antidepressant activity occurred after 1 week of treatment in some of the venlafaxine-treated patients. Significant dose-response relationships were demonstrated for both efficacy and adverse events. On the basis of the findings of this trial, most depressed outpatients should receive an adequate trial at a dosage of 75 mg/day. If the response at this dosage is not adequate, the dosage should be increased to 150 or 225 mg/day in a one- or two-step titration, respectively. The trial results suggest that a venlafaxine dosage range of 75 to 225 mg/day provides the optimum balance between efficacy and tolerability for most depressed outpatients. Some patients, however, may benefit from higher dosages (300 to 375 mg/day); they may obtain greater efficacy and an earlier response with these dosages, but they will also be more likely to experience adverse effects.

Drug names: chloral hydrate (Noctec), venlafaxine (Effexor).

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