

A Double-Blind, Placebo-Controlled Study of Venlafaxine and Fluoxetine in Geriatric Outpatients With Major Depression

Alan Schatzberg, M.D.

Steven Roose, M.D.

Background: *Despite the high prevalence of depression in elderly patients, few well-designed, placebo-controlled studies of antidepressants have been conducted in this population. This masked, placebo-controlled trial assessed the efficacy and safety of venlafaxine and fluoxetine in depressed patients older than 65 years. Method:* Three hundred patients were randomly assigned to treatment with venlafaxine immediate release (IR; $N=104$), fluoxetine ($N=100$), or placebo ($N=96$) in an eight-week trial. Venlafaxine doses were titrated from 37.5 to 225 mg per day and fluoxetine doses were titrated from 20 to 60 mg per day, as necessary, over 29 days. Efficacy variables included the 21-item Hamilton Depression Rating Scale (HAM-D₂₁) total score, HAM-D₂₁ depressed mood item score, scores on the Montgomery Åsberg Depression Rating Scale (MADRS), Clinical Global Impression–Severity of Illness (CGI-S) and Improvement (CGI-I) scales, and rates of response (based on change from baseline HAM-D or MADRS score or CGI-I score) and remission (HAM-D₁₇ ≤ 7). For the purposes of this report, efficacy analyses are focused on the HAM-D₂₁ total score. Safety assessments included monitoring of adverse events (AEs), physical examinations, vital signs assessments, laboratory determinations, and electrocardiograms. **Results:** *In all three of the treatment groups, there was a significant reduction at week 8 compared with the baseline HAM-D₂₁ total score. However, there were no significant differences among the three treatment groups on the change in HAM-D₂₁, MADRS, or CGI scores from baseline to week 8. There was no statistically significant difference in the proportion of remitters at the last on-therapy visit. The incidence of individual AEs was higher in the venlafaxine group (27%) compared with patients taking fluoxetine (19%) or placebo (9%). Conclusion:* *In this study, there was no significant difference in efficacy among placebo, venlafaxine, and fluoxetine for the treatment of depression. (Am J Geriatr Psychiatry 2006; 14:361–370)*

Key Words: Depression, venlafaxine, fluoxetine

Received June 7, 2005; revised October 4, 2005; accepted October 14, 2005. From Stanford University School of Medicine, Stanford, CA (AS); and the New York State Psychiatric Institute, New York, NY (SR). Send correspondence and reprint requests to Dr. Alan Schatzberg, Stanford University School of Medicine, 401 Quarry Rd., Rm. 300, Stanford, CA 94605-5548. e-mail: afschatz@leland.stanford.edu

© 2006 American Association for Geriatric Psychiatry

Major depression can cause significant morbidity and mortality in late life¹; if undiagnosed or inadequately treated, the illness carries both direct risks (e.g., suicide)² and indirect risks through a negative impact on the course of other major diseases prevalent in older patients (e.g., ischemic heart disease).³ Therefore, establishing safe and effective treatments for late-life depression is of compelling importance. Unfortunately, the clinical trials data for the treatment of late-life depression, particularly placebo-controlled studies, are limited. Most placebo or comparator-controlled trials of antidepressant medications in late-life major depression have important methodological limitations, including insufficient statistical power, problematic medication dosing strategies, and inadequate statistical analysis and presentation of findings.

There are five randomized, placebo-controlled trials of antidepressants in the treatment of late-life depression in which: 1) patients meet *Diagnostic and Statistical Manual of Mental Disorders, Third and Fourth Editions* criteria for major depression; 2) an adequate dose of antidepressant was administered for an adequate period of time; 3) there was an intent-to-treat outcome analysis and discussion of type II error when appropriate; and 4) at a minimum, the response rate (a <50% reduction of baseline symptoms) was reported. In these studies, the active treatments were fluoxetine,⁴ sertraline,⁵ citalopram,⁶ paroxetine,⁷ and one study had two active comparators, escitalopram and fluoxetine.⁸ In a 6-week trial that included 671 patients, the fluoxetine group had a significantly higher remission rate than the placebo group, 28% versus 18%, with remission defined as a final Hamilton Rating Scale for Depression (HAM-D)⁹ score ≤ 7 .⁴ In a study of 716 patients comparing sertraline with placebo, the rate of remission, defined as a final HAM-D ≤ 10 , was significantly greater in patients treated with sertraline (29%) compared with placebo (23%).⁵ In the third study, which randomized 178 patients to citalopram or placebo, the rate of remission, defined as final HAM-D score <10, was 35% for the citalopram and 33% for the placebo groups.⁶ In a study of 323 patients randomly assigned to paroxetine or placebo, the rate of remission, defined as a final HAM-D score of ≤ 7 , was significantly greater in patients taking paroxetine controlled-release (CR) and immediate-release (IR) (43% and 44%, respectively) than in the patients tak-

ing placebo (26%, $p=0.009$ for CR and $p=0.01$ for IR).⁷ An eight-week, randomized, double-blind trial of 517 patients compared escitalopram (10 mg/day), fluoxetine (20 mg/day), and placebo.⁸ There was no difference between the treatment groups as measured by the primary outcome measure, mean change from baseline in Montgomery Åsberg Depression Rating Scale (MADRS) total score at end point. Thus, in three of the five studies, the active medication was more effective than placebo. However, in two of the positive studies, the remission rates were low, and the differences between active medication and placebo were limited.

This article reports the results of a randomized, double-blind, placebo-controlled study comparing the efficacy of venlafaxine IR and fluoxetine with placebo in a sample of patients over the age of 65 with depression.

METHODS

The study was conducted in 21 centers (university-affiliated and private research clinics) in the United States. The protocol was reviewed and approved by the Institutional Review Boards of each study site, and the study was conducted according to the Declaration of Helsinki, Finland, and its amendments. Participants signed a written informed consent form at the time of their enrollment. The recruitment of patients was facilitated by public media announcements on radio and TV.

Patients

Inclusion Criteria. Male or female subjects aged 65 years or older and not living in a residential setting were eligible for this study. In addition, eligible participants met *Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition* criteria for unipolar depression (single or recurrent, nonpsychotic), with a current episode of at least four weeks in duration; had a 21-item HAM-D (HAM-D₂₁) score ≥ 20 at the initial visit; and were willing and able to provide informed consent. Subjects with no more than a 20% decrease in score after a single-blind, placebo lead-in week were randomized to treatment.

Exclusion Criteria

Subjects with bipolar disorder, a psychotic disorder not related to depression, current substance abuse or substance dependence within the past year (other than nicotine), current suicidal intent, Mini-Mental Status Examination score ≤ 18 , and patients who had received treatment with fluoxetine or venlafaxine in the past six months, electroconvulsive therapy within the prior three months, or any investigational drug or antipsychotic medication within the prior 30 days were excluded from the study. Also excluded were subjects who used astemizole, cisapride, sumatriptan, terfenadine, paroxetine, sertraline, or any monoamine oxidase inhibitor within 14 days, used any other antidepressant, anxiolytic, or sedative-hypnotic drug (except chloral hydrate), or any other psychotropic drug or substance within seven days of the start of the double-blind treatment period. Patients with a known hypersensitivity to venlafaxine or fluoxetine, those with clinically significant hepatic or renal disease, seizure disorder, or myocardial infarction within the prior 6 months, and patients with a severe, acute, or unstable medical illness were not allowed to participate in the study.

Study Design

The screening visit occurred one week (± 3 days) before baseline and included assessment of medical history, a psychiatric history and examination, HAM-D₂₁, physical examination, laboratory assessments, and electrocardiogram. Eligible patients entered a single-blind placebo phase, which typically lasted seven days (± 3 days). At baseline (study day zero), the HAM-D₂₁ was repeated. At the end of the placebo week, patients who had no more than a 20% decrease in HAM-D₂₁ were randomly assigned to the venlafaxine IR, fluoxetine, or placebo group. Randomization was by number in six-patient units with equal numbers of each treatment. Medication for each patient was packaged individually and code-labeled with the study number and a unique patient randomization number. Units were distributed to study sites according to the lowest available randomization number. The double-blind treatment phase was 8 weeks. Patients were seen weekly for the first four weeks of the treatment period and biweekly for

the remaining four weeks. Each visit included assessment of all efficacy and safety measures.

Study Medications

Study medications were dispensed as identically appearing capsules. Double-blind therapy was initiated as follows: venlafaxine IR was initiated as 37.5 mg once daily from study days one to four and then the dose was increased to 75 mg daily as 37.5 mg twice daily from study days five to 14. The fluoxetine dose was 20 mg once daily in the morning (with one placebo capsule in the evening) from study days one to 14. Placebo was administered twice daily (once each in the morning and evening). If clinically indicated, patients could receive up to two planned dose increases. The venlafaxine dosage could be increased on day 15 to 75 mg twice daily (150 mg/day) and again on day 29 to 112.5 mg twice daily (225 mg/day). Likewise, fluoxetine could be increased on day 15 to 40 mg in the morning (with two placebo capsules in the evening) and again on day 29 to 60 mg in the morning (with three placebo capsules in the evening). The maximum doses were 225 mg venlafaxine per day and 60 mg fluoxetine per day.

The following concomitant treatments were permitted during the study: chloral hydrate (up to 1,000 mg) or zolpidem (up to 10 mg) at bedtime as needed for sleep; nonpsychopharmacologic drugs with psychotropic effects if the patient was on a stable dose for at least one month (three months for thyroid or hormonal medications) before the start of the study; and psychotherapy, if well established before entering the study.

Efficacy and Safety Assessments

Efficacy assessments, which consisted of the HAM-D₂₁, the MADRS,¹⁰ and the Clinical Global Impression-Severity of Illness (CGI-S) and Improvement (CGI-I) scales¹¹ were performed at weeks 1, 2, 3, 4, 6, and 8 or study end point. Efficacy variables included the HAM-D₂₁ total score, HAM-D₂₁ depressed mood item, MADRS total score, CGI-S score, and CGI-I score. Although each of these variables was designated as a primary efficacy variable in the study protocol, for the purposes of this article, the primary focus will be the HAM-D₂₁ total score. Rates of response and remission were included as second-

any efficacy variables. In the a priori analysis, the following definitions were used: response was defined as a 50% or greater decrease from baseline HAM-D₂₁ total score and remission was defined as a score ≤ 7 on the first 17 items of the HAM-D₂₁ (i.e., HAM-D₁₇ score ≤ 7). After further consideration, however, it was determined that the same HAM-D scale should be used as the basis for response and remission criteria. As such, we report two sets of response rates (based on a 50% or greater decrease from baseline HAM-D₂₁ score [a priori] or HAM-D₁₇ score [post hoc]) and two sets of remission rates (based on HAM-D₁₇ ≤ 7 [a priori] or HAM-D₂₁ ≤ 7 [post hoc]). An alternative criterion, a 50% or greater decrease from baseline MADRS score, was also used to evaluate response to treatment.

Safety was evaluated on the basis of reports of adverse events and the results of physical examinations, laboratory determinations, and electrocardiograms. Adverse events were identified weekly from spontaneous patient reports or noted by the patient's caregiver or study staff.

Adverse events and vital signs were evaluated at each visit, and physical examinations, laboratory determinations, and electrocardiograms were conducted at screening and study end. The standard procedure for measuring blood pressure required instructing patients not to smoke or consume beverages containing caffeine for at least two hours before each blood pressure measurement. A mercury sphygmomanometer with a blood pressure cuff appropriate for the girth of the patient's arm was used for all blood pressure measurements. The same site personnel throughout the study took all measurements in the same arm. Patients rested for at least two minutes before the initial blood pressure reading at each visit. After the supine pulse was measured, two consecutive supine blood pressure measurements were taken two minutes apart. Patients then rose to a standing position and standing blood pressure readings were obtained after 1 minute and again two minutes later. Diastolic blood pressure was measured at the fifth Korotkoff phase (the point at which sound disappears).

Patients were monitored for sustained, treatment-emergent elevation in supine diastolic blood pressure, defined as an increase ≥ 10 mm Hg from baseline to an on-therapy value of ≥ 90 mm Hg for at least three consecutive visits.

In the event that a patient did not complete 56 days of treatment with active study drug or placebo, all safety determinations listed at day 56 were to be done on the last day the patient took his or her full dose of medication, that is, before the dose of medication is tapered, or as soon as possible thereafter.

Statistical Analysis

Efficacy analyses were performed on the intent-to-treat population, defined as all patients who took at least one dose of double-blind study medication and were evaluated for at least one primary efficacy variable (except the CGI-I scale) at baseline and once during treatment. By-visit analyses were done using observed cases (OC) and last observation carried forward (LOCF) data. For the LOCF analysis, the last available on-therapy evaluation was carried forward into all subsequent visits. Safety analyses were performed on all patients who took at least one dose of study medication. Adverse events were defined as treatment-emergent if they appeared on or after the first dose of study medication, or, if present before the first dose of study medication, they increased in severity during the study.

Statistical analyses were performed using SAS version 6.09 or 6.12 software. Unless otherwise noted, all statistical tests of significance were two-sided. $p < 0.05$ was considered statistically significant. Analysis of variance (ANOVA) was used to test for baseline comparability of treatment groups with respect to age, weight, duration of current depressive episode, the HAM-D total and depressed mood item scores, and the MADRS total score. The chi-square test was used to compare the treatment groups with respect to ethnic origin and sex.

Baseline scores on the HAM-D₂₁, HAM-D depressed mood item, MADRS, and CGI-S were compared with a one-way ANOVA using treatment group as the factor. A two-way analysis of covariance (ANCOVA), using treatment and investigator as the main factors and baseline scores as the covariate, was used to analyze data from each scheduled postbaseline visit (weeks 1, 2, 3, 4, 6, and 8). The CGI-I score, which measures change from baseline, was analyzed using ANOVA with treatment and investigator as main factors at each scheduled postbaseline visit. Response and remission rates at each scheduled visit were compared using chi-square

tests. Reported adverse events were analyzed for differences among treatment groups using the chi-square test when the incidence rate of an adverse event in any treatment group was at least 5%.

A mixed-effects model was also used in this analysis to assess the effect of time and treatment group and their interaction on the HAM-D₁₇ scores. The mixed-model analysis was done using PROC Mixed from SAS. The model used included factors of treatment group, time, and their interaction. The model was fitted with an unstructured covariance matrix.

Remission rates were calculated for all patients as well as for subgroups defined by baseline severity of depression. Baseline severity was categorized as either above or below the respective median values (21 for HAM-D, 27 for MADRS). This analysis was performed on the LOCF values using an overall among-group chi-square test as well as pairwise Fisher exact tests.

For each treatment group, vital signs (means at baseline and mean changes from baseline to final on-therapy visit) and body weights were summarized. Vital signs parameters were compared among treatment groups using two-way ANCOVA with treatment and investigator as the main factors and pretreatment value as the covariate.

RESULTS

Study Population

Patient Disposition and Demographics. A total of 300 patients were enrolled and randomly assigned to treatment: 104 to the venlafaxine group, 100 to the fluoxetine group, and 96 to the placebo group. In all, 210 patients completed the study: 67 (64%) patients in the venlafaxine group, 70 (70%) patients in the fluoxetine group, and 73 (76%) patients in the placebo group. The efficacy analysis included 288 (96%) patients from the intent-to-treat population, and the safety analysis included all patients who took study medication (N = 298 [99%]).

The overall sample was 56% female and 93% white. The mean age was 71 years (standard deviation [SD]: 5.0) and mean scores at baseline were 22 (SD: 3.0) on the HAM-D₂₁ and 27 (SD: 5.6) on the MADRS. The mean duration of the current episode for the overall population was 198 weeks, for the venlafaxine group was 149 weeks, for the fluoxetine group was 203 weeks, and for the placebo group 226 weeks. There were no statistically significant differences among the three treatment groups for any baseline or demographic characteristic (see Table 1).

TABLE 1. Baseline Patient Demographics

	Venlafaxine (N = 104)	Fluoxetine (N = 100)	Placebo (N = 96)	Test Value	p Value
Age (years), mean	71	71	71	0.62* (df = 297)	0.537
Female, %	56	45	46	2.93 [†] (df = 2)	0.231
Ethnic origin, %				8.82 [†] (df = 8)	0.358
White	93	93	93		
Black	5	5	3		
Asian	1	2	0		
Hispanic	0	0	2		
Other	1	0	2		
Weight (kg), mean	78	81	79	0.79* (df = 291)	0.456
HAM-D total score, mean	24	24	23	0.43* (df = 297)	0.649
MADRS total score, mean	26	27	27	0.50* (df = 297)	0.649
HAM-D depressed mood Item score, mean	3	3	3	0.71* (df = 297)	0.493
Duration of current episode (weeks), mean	149	203	226	1.05* (df = 295)	0.353
Patients using concomitant medications, %	91	95	95	1.45 [†] (df = 2)	0.485

*F value.

[†]Chi square.

HAM-D: Hamilton Depression Rating Scale; MADRS: Montgomery Åsberg Depression Rating Scale.

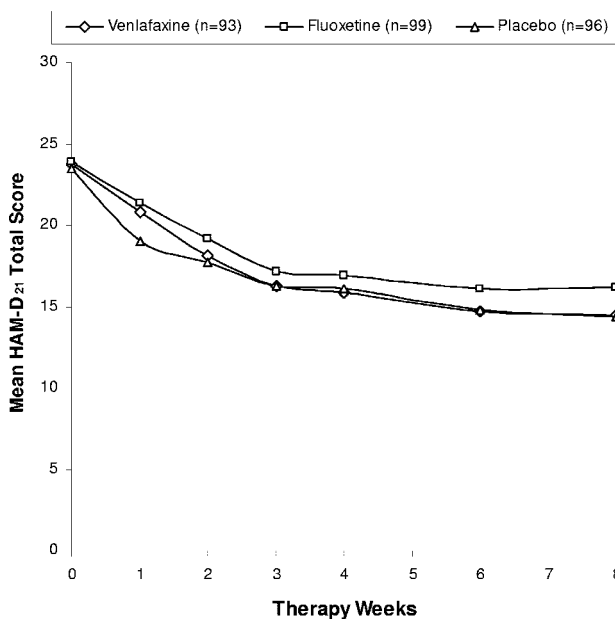
Discontinuations

No significant difference was observed in the rate of patients who discontinued treatment between treatment groups: venlafaxine (36%), fluoxetine (30%), and placebo (24%). However, the rate of discontinuation resulting from adverse events was significantly greater in the venlafaxine group (27%) compared with the placebo group (9%, $p = 0.0017$); there were not significant differences in the fluoxetine (19%) versus placebo ($p = 0.0666$) or fluoxetine versus venlafaxine comparisons ($p = 0.1838$). The rate of discontinuation resulting from unsatisfactory response was not significantly greater for the placebo group compared with the fluoxetine group (8% versus 6%, $p = 0.5874$) or for the venlafaxine (2%) versus fluoxetine comparison ($p = 0.1678$); the difference was nearly significant for the venlafaxine versus placebo comparison ($p = 0.0527$) (see Table 2).

Outcome Measures

Primary Analyses. Based on the LOCF analysis of the HAM-D₂₁ scores, there was no overall difference between groups in response or remission rates. Mean HAM-D₂₁ scores are shown in Figure 1. Analysis of the MADRS, CGI-S, and HAM-D depressed mood item scores showed similar results. There were no significant differences observed at any time point in the analysis of rates of protocol-defined response (i.e., $\geq 50\%$ decrease from baseline HAM-D₂₁ or MADRS score) and remission (i.e., HAM-D₁₇ score ≤ 7) (Figures 2–4). Similarly, the analyses of retro-

FIGURE 1. Mean HAM-D₂₁ Total Score By Visit (LOCF Data)



Notes: * $p = 0.0007$ for overall difference in treatment groups at week 1 ($F = 7.50$, $df = 261$); $p = 0.002$ placebo versus venlafaxine ($F = 10.01$, $df = 261$); $p = 0.0005$ placebo versus fluoxetine ($F = 12.38$, $df = 261$); $p = 0.794$ venlafaxine versus fluoxetine ($F = 0.07$, $df = 261$).

[†]95% Confidence interval (CI) for mean difference between groups: venlafaxine versus placebo: (-2.119, 2.191); fluoxetine versus placebo: (-0.601, 3.614); fluoxetine versus venlafaxine: (-0.587, 3.672).

spectively defined response (i.e., $\geq 50\%$ decrease from baseline HAM-D₁₇ score) and remission (i.e., HAM-D₂₁ ≤ 7) showed no significant differences (Figures 2 and 4).

TABLE 2. Primary Reasons for Discontinuation of Study (%)

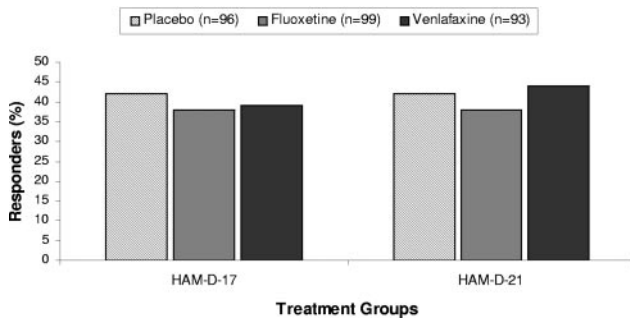
	Venlafaxine (N = 104)	Fluoxetine (N = 100)	Placebo (N = 96)	Chi Square*	p Value
Total discontinued	36	30	24	3.21	0.1997
Adverse event	27	19	9	10.14	0.0180 [†]
Failed to return	3	0	1	3.32	0.3608
Unsatisfactory response	2	6	8	4.19	0.0119 [‡]
Protocol violation	0	0	1	2.13	0.2556
Other	4	5	4	0.17	0.6982

* $df = 2$ for all comparisons.

[†] $p = 0.0017$ venlafaxine versus placebo, $p = 0.0666$ fluoxetine versus placebo, $p = 0.1838$ venlafaxine versus fluoxetine.

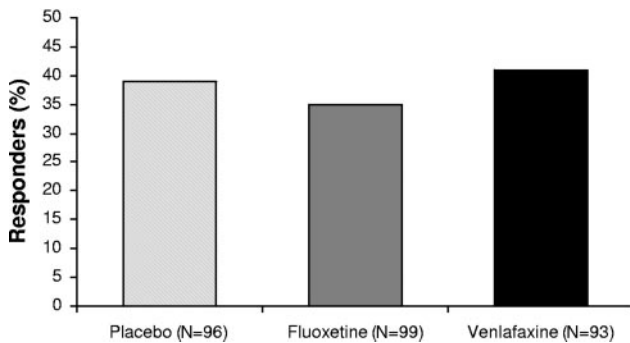
[‡] $p = 0.0527$ venlafaxine versus placebo, $p = 0.5874$ fluoxetine versus placebo, $p = 0.1678$ venlafaxine versus fluoxetine.

FIGURE 2. HAM-D Response at Endpoint



Notes: HAM-D-17 bars: chi square = 0.26, df = 2, p = 0.877; HAM-D-21 bars: chi square = 0.65, df = 2, p = 0.7220.

FIGURE 3. MADRS Response at Endpoint

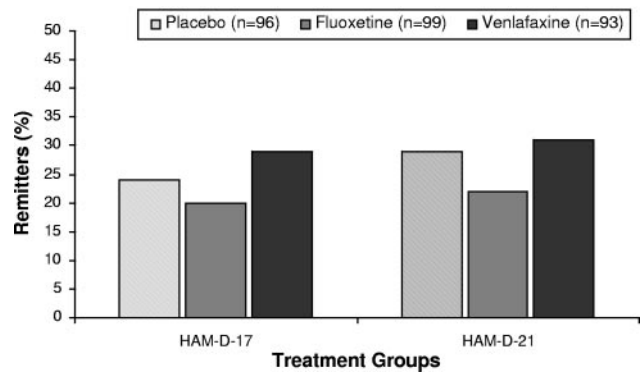


Notes: Fluoxetine: chi square = 0.62, df = 2, p = 0.732.

Post Hoc Analyses

The mixed-effects model showed no overall significant differences in remission rates among treatment groups or within subgroups for the HAM-D scores. At eight weeks, the remission rates for venlafaxine, fluoxetine, and placebo were 27%, 20%, and 24%, respectively (p = 0.549). An analysis of the subgroup with baseline HAM-D scores less than 21 revealed no overall significant differences in remission rates (33%, 33%, and 29% for venlafaxine, fluoxetine, and placebo, respectively, p = 0.870). In patients with baseline HAM-D scores of 21 or greater, there was no statistically significant difference (26%, 13%, and 20% for venlafaxine, fluoxetine, and placebo, respectively, p = 0.168).

FIGURE 4. Remission at Endpoint



Notes: HAM-D-17 bars: chi square = 2.04, df = 2, p = 0.360; HAM-D-21 bars: chi square = 2.15, df = 2, p = 0.341.

Tolerability and Safety

Adverse Events. Overall, 92% of patients taking venlafaxine, 94% of patients taking fluoxetine, and 86% of patients taking placebo reported at least one adverse event. The two most frequently reported adverse events in venlafaxine- and fluoxetine-treated patients were nausea (45% and 23%, respectively) and headache (26% and 18%, respectively); in placebo-treated patients, the most frequently reported adverse events were headache (22%) and dry mouth (15%). The drug-associated adverse events (i.e., events occurring in at least 5% of patients and at a rate of at least twice that in the placebo group) in both groups were constipation, decreased appetite, decreased libido, fatigue, insomnia, lethargy, light-headedness, limb tremor, and oversedation. Additional drug-associated adverse events in the venlafaxine group were dizziness, drowsiness, loose stools, nausea, sweating, urinary frequency, and vomiting; in the fluoxetine group, they were agitation, anxiety, coughing, decreased weight, dyspepsia, flu syndrome, irritability, nervousness, and shakiness (Table 3).

Vital Signs

Mean changes from baseline to the last on-therapy visit were calculated for each group. The venlafaxine

TABLE 3. Adverse Events Reported by $\geq 5\%$ of Patients in Any Treatment Group (%)

	Venlafaxine (N = 102)	Fluoxetine (N = 100)	Placebo (N = 96)	Chi Square*	p Value
Nausea	45 ^{§¶}	23	14	26.23	<0.001
Headache	26	18	22	2.11	0.349
Dry mouth	23 [¶]	6	15	11.20	0.004
Constipation	22 ^{§¶}	10	4	14.71	<0.001
Dizziness	17 [†]	8	5	7.88	0.019
Diarrhea	12	13	14	0.15	0.928
Fatigue	12	10	5	2.74	0.254
Dyspepsia	11	17	8	3.71	0.157
Appetite decreased	11	11	4	3.70	0.157
Sweating	11 [‡]	4	1	9.79	0.007
Insomnia	10	11	4	3.38	0.185
Oversedation	10	5	2	5.62	0.060
Libido decreased	9 [†]	8 [†]	1	6.30	0.043
Vomiting	9	2	2	7.40	0.025
Vision blurred	8	3	5	2.34	0.311
Drowsiness	8	2	3	4.65	0.098
Loose stools	7	3	2	3.33	0.189
Limb tremor	6	6	0	5.94	0.051
Eructation	6	5	5	0.08	0.959
Lightheaded	6	5	1	3.37	0.186
Urinary frequency	6	3	3	1.38	0.501
Lethargy	5	6	1	3.42	0.181
Blood pressure increased	5	4	5	0.17	0.917
Upper respiratory infection	3	6	4	1.15	0.564
Shakiness	3	5	0	4.73	0.094
Back pain	3	0 [†]	6	6.54	0.038
Anxiety	2 [¶]	10	4	6.83	0.033
Coughing	2	8	4	4.20	0.122
Agitation	2	6 [†]	0	7.06	0.029
Nervousness	2	5	2	2.02	0.365
Irritability	2	5	0	5.44	0.066
Flu syndrome	2	5	0	5.44	0.066
Weight decrease	1	6 [†]	0	8.95	0.011
Nasal congestion	0	5	3	4.94	0.085
Pruritus	0	2	5	5.93	0.052

*df = 2 for all comparisons.

Pairwise comparisons (analyzed using Fisher exact test): [†]p <0.05 versus placebo, [‡]p <0.01 versus placebo, [§]p <0.001 versus placebo, [¶]p <0.05 versus fluoxetine, [¶]p <0.01 versus fluoxetine.

group had a mean baseline supine diastolic blood pressure of 76 mm Hg and mean change of 0.50 mm Hg; the fluoxetine group had a baseline mean of 79 mm Hg and mean change of -0.61 mm Hg; and the placebo group had a baseline mean of 78.6 mm Hg and a mean change of -1.16 mm Hg. Supine systolic and standing systolic and diastolic blood pressure readings were also recorded. Five percent of the venlafaxine group (N = 5), 4% of the fluoxetine group (N = 4), and 5% of the placebo group (N = 5) showed increased blood pressure (i.e., treatment-emergent elevation from baseline in supine diastolic blood pressure of ≥ 10 mm Hg to an on therapy value of

≥ 90 mm Hg for at least three consecutive visits). One patient in each of the venlafaxine and placebo groups (1% each) and none in the fluoxetine group discontinued because of increased blood pressure. Hypertension accounted for 1% of the venlafaxine-treated patients (N = 1), 2% of the fluoxetine group (N = 2), and 0% of the placebo group prematurely discontinuing treatment. There were no prespecified mandatory criteria for increases in blood pressure that necessitated patient withdrawal from the study; the decision to reduce the dosage of study medication or to remove a patient from the study was at the discretion of the investigator.

DISCUSSION

In this randomized, placebo-controlled trial, there was no difference between either active treatment or placebo with respect to change in HAM-D score or remission rates. As anticipated, there were no differences in the discontinuation rates between active medication and placebo, but the reasons for discontinuation were significantly different. Patients on fluoxetine or venlafaxine discontinued more frequently as a result of adverse events, whereas patients on placebo had a higher rate of discontinuation because of nonresponse. It is worth noting that this study was conducted before the availability of the extended-release (XR) formulation of venlafaxine, which has a somewhat more favorable tolerability profile compared with the immediate-release formulation. Thus, the rates of adverse events associated with venlafaxine reported in this study might be higher than what would be seen in current practice, in which the XR formulation is more likely to be prescribed.

This study is a contribution to the limited literature of rigorous placebo-controlled studies of antidepressant medication for the treatment of late-life depression. There are now six placebo-controlled studies of medication treatment in late-life depression. In three studies, medication was more effective than placebo, and in three studies, there was no difference between medication and placebo, including the two studies in which there were two active medication treatments. The remission rates to medication range from 28% to 43% and the remission rates for placebo range from 18% to 40%. One of the problems in comparing studies is the different criteria used to define remission, which varied in terms of the version of the HAM-D used, the final HAM-D score, or whether an HAM-D or the MADRS was used for remission criteria.

Thus, where does this leave the clinician who values evidence-based treatment recommendations for late-life depression? First, a failure to find a difference between medication and placebo in a clinical trial should not be interpreted as meaning that it is just as effective to do nothing as to give medication. As has been argued previously, being randomized to receive placebo is not remotely close to receiving no treatment. Patients receiving placebo also participate in interactions with the physician and other members

of the research staff that may have nonspecific therapeutic effects. The components of clinical management received by patients in the placebo group are not only more than "no treatment," but are also more than that received by a patient in standard clinical care, e.g., the frequency and duration of visits, free medication, medical evaluation, and so on. Therefore, if the clinician wants to replicate the response rate of placebo condition, they must replicate the treatment received by the patients receiving placebo. In reality, the clinical applicability of placebo treatment is limited.

Second, although the available data are limited, with respect to both the percentage of trials in which medication is more effective than placebo and the rates of remission, to date, the results of placebo-controlled trials of antidepressant medication in older patients are comparable to the results of trials in younger depressed patients.

Third, the rates of medication response in trials that compare two active treatments range from 41% to 93% with a mean of 63%, which are significantly higher than the rates of response when the same medications are studied in a placebo-controlled trial (range: 28%–43%; mean: 42%). Although comparator-controlled trials cannot establish the efficacy of a treatment, the conditions of a comparator trial more closely resemble the clinical situation, i.e., the patient and doctor know that the patient is receiving an active treatment. It could be argued that the results of studies that compare two active treatments may better reflect the results that can be anticipated in clinical practice.

There are other treatments that are either established or widely believed to be effective for the treatment of late-life depression, notably some specific psychotherapies and electroconvulsive therapy (ECT). ECT response rate is not adversely affected by increasing age and the current standards for optimal administration of ECT minimize cognitive side effects. However, effective ECT treatment requires continuation medication to sustain response. Clinical trials support the efficacy of specific psychotherapies, cognitive behavior, problem-solving, and interpersonal therapy for the treatment of late-life depression, but these studies do not include a psychotherapy–placebo control group.

Thus, perhaps a reasonable, albeit somewhat frustrating, conclusion is that currently there is insuffi-

cient data to allow for evidence-based practice for the treatment of late-life depression. Therefore, there remains a compelling need to do more systematic studies of antidepressant treatments in this vulnerable yet understudied population.

Funding for this study provided by Wyeth Research.

The authors would like to acknowledge Sherri D. Jones, Pharm.D.; Mary E. Hanson, Ph.D.; and Bernard B. Tulsı, M.Sc., for their editorial assistance.

References

1. Beekman AT: Depression and medical illness in later life. *Prim Care* 2000; 2Supplement(suppl 5):9-14
2. Lebowitz BD, Pearson JL, Schneider LS, et al: Diagnosis and treatment of depression in late life. Consensus statement update. *JAMA* 1997; 278:1186-1190
3. Hippisley-Cox J, Fielding K, Pringle M: Depression as a risk factor for ischaemic heart disease in men: population based case-control study. *BMJ* 1998; 316:1714-1719
4. Tollefson GD, Bosomworth JC, Heiligenstein JH, et al: A double-blind, placebo-controlled clinical trial of fluoxetine in geriatric patients with major depression. The Fluoxetine Collaborative Study Group. *Int Psychogeriatr* 1995; 7:89-104
5. Schneider LS, Nelson JC, Clary CM, et al: An 8-week multicenter, parallel-group, double-blind, placebo-controlled study of sertraline in elderly outpatients with major depression. *Am J Psychiatry* 2003; 160:1277-1285
6. Roose SP, Sackeim HA, Krishnan KR, et al: Antidepressant pharmacotherapy in the treatment of depression in the very old: a randomized, placebo-controlled trial. *Am J Psychiatry* 2004; 161: 2050-2059
7. Rapaport MH, Schneider LS, Dunner DL, et al: Efficacy of controlled-release paroxetine in the treatment of late-life depression. *J Clin Psychiatry* 2003; 64:1065-1074
8. Reines EH, Andersen HF, de Swart H, et al: Tolerability of escitalopram in the treatment of depressed elderly patients. Poster presented at the 45th Annual Meeting of the Scandinavian College of Neuropsychopharmacology, Juan-Les-Pins, France, 2004
9. Hamilton M: A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960; 23:56-62
10. Montgomery SA, Asberg M: A new depression scale designed to be sensitive to change. *Br J Psychiatry* 1979; 134:382-389
11. Guy W: 028 CGI Clinical Global Impressions, in ECDEU Assessment Manual for Psychopharmacology, Revised 1976. U.S. Department Health, Education and Welfare, National Institute Mental Health, 1976, pp 217-222
12. Roose SP, Glassman AH, Attia E, et al: Comparative efficacy of selective serotonin reuptake inhibitors and tricyclics in the treatment of melancholia. *Am J Psychiatry* 1994; 151:1735-1739