Randomized, Double-Blind Comparison of Venlafaxine and Fluoxetine in Outpatients With Major Depression

Jorge Costa e Silva, M.D.

Background: This was an 8-week, multicenter, randomized, double-blind, parallel-group study of the efficacy and tolerability of venlafaxine and fluoxetine.

Method: Outpatients with DSM-III-R major depression, a minimum score of 20 on the 21-item Hamilton Rating Scale for Depression (HAM-D), and depressive symptoms for at least 1 month were eligible. Patients were randomly assigned to treatment with venlafaxine, 37.5 mg twice daily, or fluoxetine, 20 mg once daily. The dose could be increased to venlafaxine, 75 mg twice daily, or fluoxetine, 20 mg twice daily, after 3 weeks for a poor response. The primary efficacy variables were the final on-therapy scores on the HAM-D, Montgomery-Asberg Depression Rating Scale (MADRS), and Clinical Global Impressions Severity of Illness (CGI-S) and Improvement (CGI-I) scales.

Results: Three hundred eighty-two patients were randomly assigned to therapy and included in the intent-to-treat analysis. Both venlafaxine and fluoxetine produced significant reductions from baseline to day 56 in mean HAM-D, MADRS, and CGI-S scores, but no significant differences were noted between groups. Among patients who increased their dose at 3 weeks, significantly ($p < .05$) more patients taking venlafaxine than taking fluoxetine had a CGI-I score of 1 (very much improved) at the final evaluation. The most frequent adverse events were nausea, headache, and dizziness with venlafaxine and nausea, headache, and insomnia with fluoxetine.

Conclusion: These results support the efficacy and tolerability of venlafaxine in comparison with fluoxetine for treating outpatients with major depression.

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Contributions of the following investigators are acknowledged: Study Coordinator: Jorge Alberto Costa e Silva, M.D., World Health Organization. Brazil: *Helena Maria Calil, M.D., Universidade Federal de São Paulo, São Paulo; Juarez Oliveira Castro, M.D., Universidade Federal de Minas Gerais, Minas Gerais; Márcio Versiani, M.D., Universidade Federal do Rio de Janeiro, and Sandra I. Ruschell Siffert, M.D., Santa Caso do Rio de Janeiro, Rio de Janeiro; and William A. Dunningham, M.D., Universidade Federal de Bahia, Bahia.* Argentina: *Carlos Collazo, M.D., Eduardo Mendizabal, M.D., Hector Jorge Bertera, M.D., Manuel Suarez Richards, M.D., and Sergio Rojtemberg, M.D., Universidad de Buenos Aires, Buenos Aires.* Chile: *Graciela Rojas, M.D., and Hernán Silva, M.D., Universidad de Chile, Santiago; Pedro Retamal, M.D., Hospital del Salvador, Santiago; Rodrigo Labarcda, M.D., Universidad Catalica de Chile, Santiago; and Rosemarie Fritsch, M.D., Hospital Dr. José Horwitz Barak, Santiago.* Colombia: *Jaime Vengoechea, M.D., and Nestor Fajardo, M.D., Pontificia Universidad Javariana de Bogotá, Bogotá; and Ricardo José Toro, M.D., Universidad Antioquia Medellin, Medellin.* Uruguay: *Ariel Montalban, M.D., and Eugenio Bayardo, M.D., Universidad de La República, Montevideo.* Venezuela: *Antonio Pacheco, M.D., Universidad de Caracas, Caracas.*

Reprint requests to: Jorge Costa e Silva, M.D., University of Rio de Janeiro, University Hospital, Rua Getulio das Neves, 22, Rio de Janeiro 22461, Brazil.

The epidemiology of major depression in Latin America closely parallels that in North America and other Western societies.[1] However, some differences in the symptoms of depression have been identified between North and South American patients with major depression.[2] Most notably, depressed patients in South America have exhibited depression of greater severity and a higher incidence of physical symptoms and somatization than those in North America.[2] Despite these differences, a similar response to antidepressant therapy has been observed.[3]

The newer antidepressants, including selective serotonin reuptake inhibitors (SSRIs) and dual-action antidepressants such as venlafaxine, a selective serotonin/norepinephrine reuptake inhibitor (SNRI), are gradually replacing tricyclic antidepressants (TCAs) as the drugs of choice for treating major depression and other mood disorders because of poor long-term tolerability and safety concerns with the TCAs. Despite the widespread use of SSRIs, questions have arisen about their efficacy, especially in hospitalized patients with severe, melancholic depression.[4,5] Some authors have suggested that the benefits of antidepressants with a dual rather than single

mechanism of action may include a more robust response in a broader range of patients.[6] Evidence from controlled clinical trials with venlafaxine supports the hypothesis of similar efficacy at usual clinical doses[7] but a more robust clinical response at higher doses.[8,9]

Studies conducted in Latin America of the efficacy and tolerability of venlafaxine in comparison with an SSRI previously have not been reported. Therefore, the purpose of this double-blind, randomized study was to compare the efficacy and tolerability of flexible dosage regimens of venlafaxine and fluoxetine in outpatients with major depression.

METHOD

This was a prospective, randomized, double-blind, parallel-group study conducted at clinical sites in Argentina, Brazil, Chile, Colombia, Uruguay, and Venezuela to compare the efficacy and safety of venlafaxine and fluoxetine in outpatients with major depression. The study was conducted in accordance with the Declaration of Helsinki. The protocol was approved by the appropriate institutional ethics committees at each clinical site, and written informed consent was obtained from patients prior to enrollment.

Patient Selection

Outpatients aged 18 to 60 years were eligible if they met DSM-III-R criteria for major depression, had a minimum baseline score of 20 on the 21-item Hamilton Rating Scale for Depression (HAM-D)[10] with a decrease of not more than 20% between screening and baseline, and had symptoms of depression for at least 1 month before study entry. Women of childbearing potential were required to have a negative plasma pregnancy test (human β-chorionic gonadotropin) and to use an oral contraceptive, intrauterine device, or barrier method of contraception during the entire study.

Patients were excluded if they had known sensitivity to venlafaxine or fluoxetine. Those patients with a history of any clinically significant cardiac, hepatic, or renal disease or clinically significant abnormalities on a screening physical examination, electrocardiogram (ECG), or laboratory tests were excluded. Also excluded were patients with acute suicidal tendencies, a history of a seizure disorder, history or presence of any psychotic disorder not associated with depression, or history of drug or alcohol dependence within the past year. Patients were not eligible if they were using any investigational drug, fluoxetine, antipsychotic drug, neuroleptic drug, or electroconvulsive therapy within 30 days; a monoamine oxidase inhibitor or paroxetine within 14 days; any other antidepressant, anxiolytic, sedative-hypnotic drug (except zopiclone), or psychotropic drug or substance within 7 days before baseline; or any nonpsychotropic drug with psychotropic effects unless the dosage had been stable for a minimum of 1 month prior to treatment. Introduction or change in intensity of psychotherapy was not permitted during the study period.

Study Procedure

At a screening visit conducted within 7 days before baseline, eligible outpatients underwent a prestudy evaluation that included a complete medical and psychiatric history (HAM-D, the Montgomery-Asberg Rating Scale [MADRS],[11] the Clinical Global Impressions [CGI] scale[12]), a complete physical examination, monitoring of vital signs, standard clinical laboratory testing and urine drug screen, and a 12-lead ECG.

Patients satisfying selection criteria were randomly assigned to either venlafaxine, 37.5 mg twice daily, or fluoxetine, 20 mg once daily. Beginning on day 22, the dosage could be increased to venlafaxine, 75 mg twice daily, or fluoxetine, 20 mg twice daily, at the investigators' discretion if clinically indicated to improve the response. From day 22, doses were maintained within the range of 37.5 to 75 mg twice daily for venlafaxine and 20 mg once or twice daily for fluoxetine. At the end of the treatment period, venlafaxine and fluoxetine were tapered over 7 days. Patients were permitted to take zopiclone 7.5 mg at bedtime for sleep, but other psychotropic medications were prohibited.

Study Assessments

The HAM-D, MADRS, and CGI assessments were administered at baseline and on days 7, 14, 21, 28, 42, and 56. The Hopkins Symptom Checklist (SCL-61 or SCL-90)[13] was administered at baseline and on days 28 and 56. Patients were examined and questioned regarding any adverse symptoms. Safety evaluation was based on reports of study events, concomitant medication records, vital signs, weight, ECG, and laboratory tests. A study event was defined as any adverse event experienced by a patient at any time during the study, including treatment-emergent signs or symptoms, a new intercurrent illness, or clinically significant changes in any laboratory test, vital signs, weight, or ECG. Treatment-emergent study events were new adverse events or those that worsened during treatment.

Statistical Analysis

The primary efficacy variables were the final on-therapy scores for the 21-item HAM-D, MADRS, and CGI Severity of Illness (CGI-S) and Improvement (CGI-I) scales. A response was defined as a decrease in the HAM-D or MADRS total score of at least 50% from baseline to the final evaluation or a CGI-I score of 1 (very much improved) or 2 (much improved). A global response was defined as a HAM-D or MADRS response and a CGI-I response. A sustained response was a response that once observed persisted to the end of the study and lasted for at least 2 weeks. Patients who withdrew before study

Table 1. Baseline Demographic and Clinical Characteristics*

Characteristic	Venlafaxine (N = 196)	Fluoxetine (N = 186)	p Value
Sex (female:male)[a]	157:38	144:41	.521
Age, y (mean ± SD)	40.5 ± 10.7	39.8 ± 10.3	.532
Range	18–60	18–60	
Previous history of depression	79.6%	76.3%	.444
Duration of current episode, wk (mean ± SD)	28.8 ± 44.9	31.7 ± 47.8	.544
Previous antidepressant use	34.9%	31.2%	.443
HAM-D (mean ± SD)	30.4 ± 6.2	29.7 ± 5.3	.556
MADRS (mean ± SD)	33.9 ± 6.0	33.8 ± 5.6	.898
CGI-S, N (%)[b]			.350
Mildly ill or better (3)	5 (2.6)	6 (3.3)	
Moderately ill (4)	65 (33.7)	66 (36.3)	
Markedly ill (5)	83 (43.0)	79 (43.4)	
Severely ill (6)	39 (20.2)	31 (17.0)	
Extremely ill (7)	1 (0.5)	0 (0.0)	
SCL-61 (mean ± SD)	151.0 ± 27.7	147.0 ± 24.1	.214
SCL-90 (mean ± SD)	245.8 ± 67.3	241.5 ± 49.0	.698

*Abbreviations: CGI-S = Clinical Global Impressions Severity of Illness scale, HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale, SCL = Symptom Checklist.
[a]Data missing on 1 patient in each group.
[b]Data not available for 3 patients taking venlafaxine and 4 taking fluoxetine.

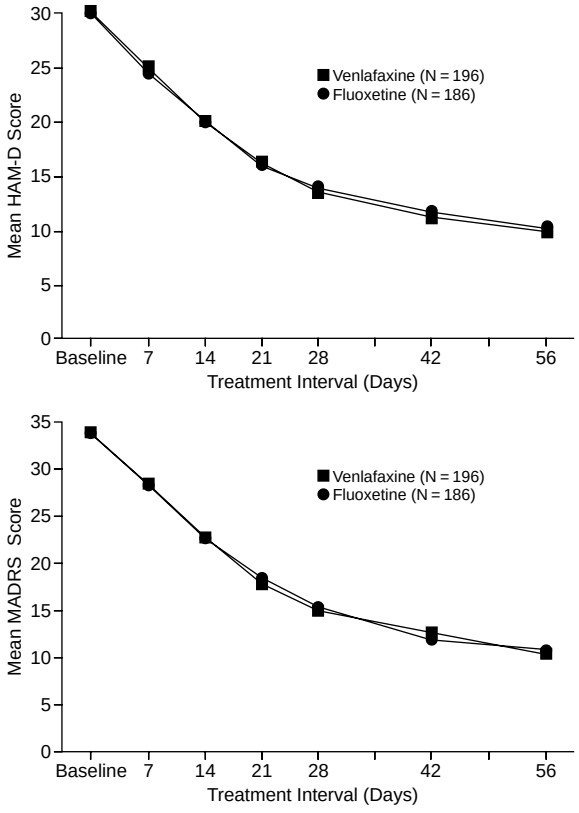
Table 2. Reasons for Premature Withdrawal From the Study

	Venlafaxine (N = 196)		Fluoxetine (N = 186)	
Reason	N	%	N	%
Any reason	29	14.8	18	9.7
Adverse reaction	14	7.4	7	3.8
Other medical/nonmedical event	2	1.0	2	1.1
Failed to return	6	3.1	5	2.7
Protocol violation	0	0.0	0	0.0
Patient/subject request	2	1.0	2	1.1
Unsatisfactory response/efficacy	5	2.6	2	1.1

completion had efficacy assessments performed on the last day of study medication. A post-study evaluation also was administered 7 days after study medication was discontinued. Efficacy analyses were performed on an intent-to-treat basis using a last-observation-carried-forward (LOCF) method. All tests were 2-sided at an alpha level of .05 with 85% power.

The Fisher exact test or chi-square analysis was used to compare baseline characteristics, such as sex, concurrent diagnoses, and concomitant medications; and analysis of variance (ANOVA) was used to compare baseline continuous variables such as age, weight, and baseline HAM-D, MADRS, CGI-S, SCL-61, and SCL-90 scores. Scores on the HAM-D, MADRS, CGI-I, and CGI-S scales and vital signs and laboratory values were assessed at each visit using a 2-way analysis of covariance (ANCOVA) or ANOVA with treatment, center, and their interaction as factors and the baseline score as a covariate. The t test or Wilcoxon signed rank test was used to assess

Figure 1. Mean HAM-D and MADRS Scores for Patients Treated With Either Venlafaxine or Fluoxetine



significant changes over time. Chi-square analysis was used for comparisons of response rates between groups and for comparing the proportion of patients discontinuing and the incidence of study events.

RESULTS

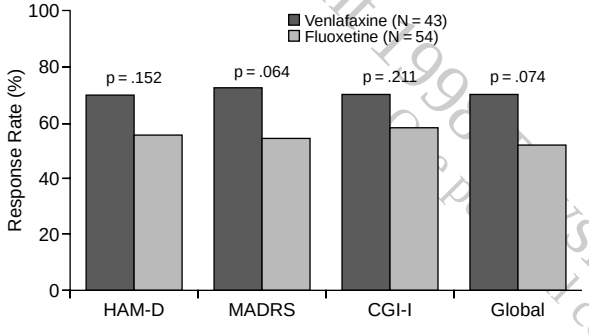
Three hundred eighty-two patients were randomly assigned to study medication and included in the intent-to-treat analyses, 196 taking venlafaxine and 186 taking fluoxetine. The 8-week study was completed by 335 patients. Baseline demographic and clinical characteristics were comparable between treatment groups (Table 1). Twenty-nine (14.8%) patients in the venlafaxine group and 18 (9.7%) in the fluoxetine group withdrew before the end of the study (p = .128) (Table 2).

The HAM-D and MADRS scores decreased significantly (p < .05) from baseline to the end of treatment in both venlafaxine and fluoxetine groups (Figure 1). However, there were no significant differences between treatment groups at any time point on the HAM-D and MADRS scales. There were no significant differences between venlafaxine and fluoxetine treatment groups in changes from baseline for the CGI-S or CGI-I scores. The proportion of patients with a normal CGI-S score at day

Table 3. Most Common (≥ 5%) Treatment-Emergent Adverse Effects Occurring During the First Week of Treatment With Venlafaxine or Fluoxetine

	Venlafaxine (N = 194)		Fluoxetine (N = 185)	
Adverse Effect	N	%	N	%
Nausea	56	28.9	35	18.9
Headache	22	11.3	13	7.0
Dizziness	16	8.3	6	3.2
Somnolence	16	8.3	3	1.6
Trembling	16	8.3	3	1.6
Diaphoresis	15	7.7	2	1.1
Anxiety	14	7.2	8	4.3
Dry mouth	14	7.2	6	3.2
Insomnia	12	6.2	15	8.1

Figure 2. HAM-D, MADRS, CGI Improvement (CGI-I), and Global Response Rates Among Patients Taking an Increased Dose of Venlafaxine (150 mg/day) or Fluoxetine (40 mg/day)

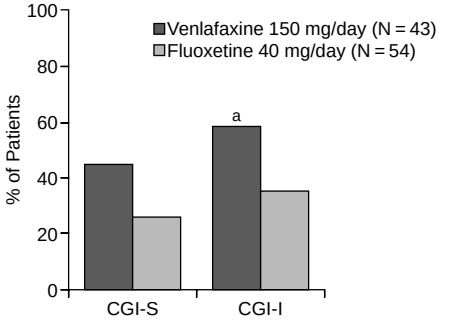


56 was 54.6% in the venlafaxine group and 50.4% in the fluoxetine group. Similarly, the proportion of patients with a CGI-I score of 1 (very much improved) or 2 (much improved) at day 56 was 80.6% with venlafaxine and 83.9% with fluoxetine. A global response (≥ 50% decrease in HAM-D or MADRS score and CGI-I score of 1 or 2) was observed in 86.8% with venlafaxine and 82.0% with fluoxetine. A remission (score of 8 or less on the first 17-items of the HAM-D) was observed in 60.2% of patients in each group.

Scores on the SCL-61 (assessed in Latin America) and SCL-90 (assessed in Brazil) decreased significantly ($p < .05$) from baseline to day 56 with both venlafaxine and fluoxetine, but no significant differences were observed between groups.

An analysis was performed of the response among patients who increased their dose of venlafaxine to 150 mg/day or fluoxetine to 40 mg/day after 3 weeks. Forty-three patients in the venlafaxine group and 54 in the fluoxetine group increased their dose after 3 weeks. No significant differences were observed between these high-dose venlafaxine and fluoxetine groups for baseline characteristics or for mean HAM-D, MADRS, CGI-S, or CGI-I scores. However, a trend for superiority of venlafaxine over fluoxetine was observed for the HAM-D,

Figure 3. Proportion of Patients With a Score of 1 on the CGI-S (Normal) or CGI-I (Very Much Improved) Scales Among Patients Taking an Increased Dose



[a]$p < .05$, chi-square test.

MADRS, CGI-I, and global response rates (Figure 2). A comparison of the proportion of patients achieving a score of 1 on the CGI-S or CGI-I scales at the final evaluation showed a significantly ($p < .05$) higher proportion of venlafaxine-treated patients with a CGI-I score of 1 (very much improved) (Figure 3). A remission was recorded in 48.8% of venlafaxine-treated patients and in 35.2% of fluoxetine-treated patients ($p = .175$).

Safety

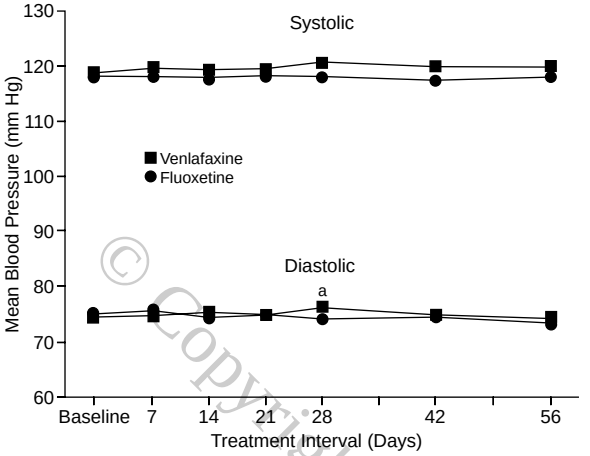
Treatment-emergent adverse events were reported in 69.4% of venlafaxine-treated patients and 65% of fluoxetine-treated patients (Table 3). Fourteen patients taking venlafaxine and 7 taking fluoxetine discontinued prematurely because of adverse events ($p = .147$). The most common adverse events with venlafaxine were nausea, headache, dizziness, somnolence, and trembling and with fluoxetine were nausea, headache, insomnia, anxiety, and appetite decrease. There were no significant differences between groups for specific adverse events. The incidence of nausea, dizziness, insomnia, and somnolence decreased consistently over time with venlafaxine. With fluoxetine, the incidence of nausea decreased over time, but the incidence of anxiety and headache remained constant or increased over time.

There were no clinically significant changes from baseline in laboratory values in either venlafaxine or fluoxetine groups. At day 28, mean standing diastolic blood pressure was 75.7 mm Hg with venlafaxine and 74.2 mm Hg with fluoxetine ($p = .037$); mean supine diastolic blood pressure was 76.3 mm Hg with venlafaxine and 74.2 mm Hg with fluoxetine ($p = .017$; Figure 4). Other statistically significant differences between treatment groups in vital signs, weight, or ECG were not observed.

DISCUSSION

The results from this trial showed that, overall, venlafaxine and fluoxetine were comparable in efficacy and

Figure 4. Mean Supine Systolic and Diastolic Blood Pressure Over Time With Venlafaxine and Fluoxetine



[a]p = .017 for venlafaxine vs. fluoxetine.

tolerability for the treatment of outpatients with major depression. Nevertheless, among the subgroup of patients who increased their dosage after the third week for an inadequate response, there was a consistent trend for an improved response with venlafaxine, demonstrating differences of 12% to 16% between treatment groups, and when a CGI-I score of 1 was the criterion, a statistically significant difference was observed.

Previously, results from clinical trials with venlafaxine have demonstrated its effectiveness in the treatment of major depression in a wide range of depressed patients including hospitalized patients and outpatients, the elderly, those with melancholic symptoms, and patients with psychomotor agitation/retardation over a wide range of doses.[7–9,14–18] Although 50% to 60% of patients respond to the recommended dose of venlafaxine, 75 mg/day,[7,9] others have reported a more robust response when the dose of venlafaxine was increased to 150 mg/day or more.[8,9]

Venlafaxine and fluoxetine exhibited similar tolerability profiles. Nausea was the most common adverse event with both venlafaxine and fluoxetine, as has been reported in other clinical trials.[7,9] The incidence of nausea was highest during the first week with venlafaxine and fluoxetine but decreased over time in both groups. The incidence of other common adverse events, including dizziness and insomnia, also decreased over time with venlafaxine. In contrast, the incidence of anxiety and headache with fluoxetine was initially high and remained at constant levels throughout the trial. An increase in anxiety and agitation has been noted with fluoxetine in other controlled trials.[19,20] An increase in blood pressure previously has been reported with venlafaxine at doses above 200 mg/day.[21] Although a statistically significant increase in blood pressure was reported in this trial with venlafaxine at the fourth week, the mean absolute increase was approximately 2 mm Hg.

Increasingly, the SSRIs are being used as first-line therapy over TCAs for treating major depression. However, questionable efficacy in some groups of patients with more severe disease, the absence of a dose-response effect, and the potential for clinically significant drug-drug interactions with many commonly used drugs may hinder their efficacy and tolerability.[4,5,22–26] These first 2 limitations, namely limited efficacy and the lack of a dose-response effect, have been hypothesized as being due to the single mechanism of action of SSRIs.[6]

In summary, the results from this comparative study indicate that, overall, venlafaxine and fluoxetine exhibited comparable efficacy and tolerability for treating major depression. However, among patients requiring higher doses, a better response to venlafaxine was observed that was most apparent when stringent criteria for response were applied.

Drug names: fluoxetine (Prozac), paroxetine (Paxil), venlafaxine (Effexor).

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