Randomized, Double-Blind Comparison of Venlafaxine and Sertraline in Outpatients With Major Depressive Disorder

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Background: This 8-week, double-blind, randomized trial compared the efficacy and tolerability of venlafaxine and sertraline in patients with major depression.

Method: Outpatients (N = 147) with DSM-IV major depressive disorder and a baseline 21-item Hamilton Rating Scale for Depression (HAM-D) score of at least 18 were randomly assigned to venlafaxine, 37.5 mg b.i.d., or sertraline, 50 mg once daily. From day 15, the doses could be increased to venlafaxine, 75 mg b.i.d., or sertraline, 50 mg b.i.d. Efficacy was assessed with the 21-item HAM-D, the Montgomery-Asberg Depression Rating Scale (MADRS), and the Clinical Global Impressions scale (CGI) using a modified intent-to-treat analysis.

Results: No significant differences were noted between treatments for mean HAM-D, MADRS, or CGI scores. At week 8, the HAM-D response rate was 83% with venlafaxine (N = 75) and 68% with sertraline (N = 72) (p = .05). A HAM-D score less than 10 was recorded in 68% of venlafaxine-treated and 45% of sertraline-treated patients at week 8 (p = .008). Among patients who increased their dose, the remission rate (HAM-D score < 10) was 67% with venlafaxine and 36% with sertraline at week 8 (p < .05). The overall discontinuation rate was 21% with venlafaxine and 17% with sertraline. The most common adverse events with venlafaxine were nausea, headache, and sweating and with sertraline were nausea, headache, and diarrhea.

Conclusion: Among patients who increased their dose, approximately twice as many experienced a remission with venlafaxine, which is a more clinically relevant endpoint than response and represents the proportion of patients who have recovered or are well.

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Venlafaxine has previously been shown to be effective in the treatment of major depression in both outpatients and hospitalized patients. Comparative studies with fluoxetine, paroxetine, and tricyclic antidepressants have demonstrated efficacy equal to or better than that of venlafaxine.[1–7] At doses of 150 mg/day or higher, venlafaxine has demonstrated greater efficacy than fluoxetine, 20 or 40 mg/day, in depressed patients.[1–3] Similarly, a comparison of venlafaxine and paroxetine in patients failing at least 2 previous antidepressant treatments showed that venlafaxine at higher doses was significantly more effective than paroxetine, 30 to 40 mg/day.[4]

The efficacy and tolerability of sertraline have been demonstrated in patients with major depression.[8,9] The minimum effective dose of sertraline is 50 mg/day, and a flat dose-response curve over the range from 50 to 200 mg/day is seen.[10] In contrast, venlafaxine exhibits a dose-response effect over the usual dosage range.[11,12] The efficacy and tolerability of venlafaxine and sertraline have previously not been compared in a randomized, controlled clinical trial of patients with major depression. The objective of this study, therefore, was to compare the efficacy and tolerability of venlafaxine and sertraline in outpatients with major depression.

METHOD

This 8-week randomized, double-blind, multicenter trial compared the efficacy and tolerability of venlafaxine and sertraline in outpatients with major depression. Appropriate ethics committees approved the study protocol, and the study was conducted in accordance with the principles of the Declaration of Helsinki. Patients provided written informed consent prior to enrollment.

Patient Selection

Patients aged 18 to 65 years were eligible if they met DSM-IV criteria for major depressive disorder, had a

minimum baseline score of 18 on the 21-item Hamilton Rating Scale for Depression (HAM-D)[13] with a decrease of not more than 20% between screening and baseline, and had symptoms of depression for at least 14 days before study entry. Women of childbearing potential were required to have a negative urine pregnancy test and to use a medically acceptable method of contraception during the study.

Patients with a known sensitivity to venlafaxine or sertraline or with a history of any clinically significant cardiac, hepatic, or renal disease or clinically significant abnormalities at a screening examination 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 2 years. Patients were precluded from participation if they were using any investigational drug, antipsychotic drug, neuroleptic drug, or electroconvulsive therapy within 30 days; fluoxetine within 21 days; a monoamine oxidase inhibitor or other antidepressant within 14 days; or a benzodiazepine (except oxazepam or temazepam) or other anxiolytic or sedative hypnotic within 7 days of baseline. Use of any nonpsychotropic drug with psychotropic effects was precluded unless the dosage had been stable for at least 1 month prior to treatment.

Study Procedure

At a screening visit conducted within 7 days of baseline, eligible patients underwent a prestudy evaluation that included a complete medical and psychiatric history with administration of the HAM-D and a complete physical examination including weight, clinical laboratory testing (hematology, blood chemistry, prothrombin time, urinalysis, and urine drug screen), and a 12-lead electrocardiogram (ECG).

Patients satisfying selection criteria were randomly assigned to either venlafaxine, 37.5 mg twice daily, or sertraline, 50 mg once daily in the morning and placebo in the evening. On day 15, the dosage could be increased to venlafaxine, 75 mg twice daily, or sertraline, 50 mg twice daily, at the investigators' discretion if clinically indicated to improve the response. At the end of the treatment period, venlafaxine and sertraline were tapered over 7 days. Patients were permitted to take oxazepam, 30 to 75 mg/day, or temazepam, up to 20 mg/day, at bedtime for sleep.

Study Assessments

The HAM-D, the Montgomery-Asberg Depression Rating Scale (MADRS),[14] and the Clinical Global Impressions scale (CGI)[15] were administered at baseline and on days 7, 14, 28, 42, and 56. The UKU Side Effect Rating Scale[16] was administered on days 7, 14, 28, 42, 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 scores on the 21-item HAM-D, MADRS, and CGI-Severity of Illness scale (CGI-S). A response was defined as a decrease in the HAM-D or MADRS total score of at least 50% from baseline or a CGI-Improvement scale (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 response. Remission was defined as a HAM-D score < 10. 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 completion had efficacy assessments performed on the last day of study medication. Efficacy analyses were performed on a modified intent-to-treat basis, which included all patients randomly assigned to treatment who received at least 1 dose of study drug and had at least 1 efficacy assessment. The study was designed to detect a difference of 8 between treatments in the MADRS total score with 80% power using a 2-sided test at the 5% significance level.

The Fisher exact test was used to compare baseline characteristics such as sex, concurrent diagnoses, and concomitant medications, and analysis of variance (ANOVA) was used to compare baseline variables such as age, weight, and baseline HAM-D, MADRS, and CGI-S scores. Scores on the HAM-D, MADRS, and CGI-S were assessed at each visit using a 2-way analysis of covariance (ANCOVA) with treatment, center, and their interaction as factors and the baseline score as a covariate. The Fisher exact test was used for comparisons of response rates between groups and for comparing the proportion of patients discontinuing and the incidence of study events. The UKU was analyzed in 4 parts: psychic, neurologic, autonomic, and sexual, which was analyzed separately for men and women using logistic methods stratified for the baseline assessment.

RESULTS

In total, 75 patients were randomly assigned to venlafaxine and 72 to sertraline. No significant differences were noted between groups for baseline demographic and clinical characteristics (Table 1). Sixteen patients (21%) taking venlafaxine and 12 (17%) taking sertraline discontinued treatment prematurely (Table 2). The most com-

Table 1. Baseline Demographics and Clinical Characteristics of Patient Sample[a]

Characteristic	Venlafaxine	Sertraline
Patients, N	75	72
Sex (M/F)	26/49	24/48
Age, y	44.1 ± 11.4	41.0 ± 10.7
Range, y	19–71	20–63
Weight, kg	74.6 ± 14.5	72.3 ± 16.2
Weeks of depression,[b] %		
0–4	4	4
5–13	37	44
14–26	25	18
27–52	12	15
53–104	8	7
> 104	9	7
MADRS total score	27.8 ± 6.0	28.1 ± 5.1
HAM-D total score	25.5 ± 3.5	25.8 ± 4.5
CGI-S score,[c] %		
Moderately ill (4)	53	58
Markedly ill (5)	39	32
Severely ill (6)	7	8
Extremely ill (7)	1	0

[a]Unless otherwise stated, data are given as mean ± SD. Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale.
[b]5% (N = 4) venlafaxine and 5% (N = 4) sertraline were unknown.
[c]Numbers in parentheses indicate ratings. Data on 1 patient missing.

Table 2. Reasons for Discontinuation[a]

	Venlafaxine (N = 75)		Sertraline (N = 72)	
Reason	N	%	N	%
Any reason	16	21	12	17
Adverse event	12	16	5	7
Unsatisfactory response/efficacy	6	8	4	6
Failed to return	3	4	2	3
Other medical/nonmedical event	0	0	3	4
Patient request	1	1	1	1
Protocol violation	1	1	2	3

[a]More than one reason was allowed.

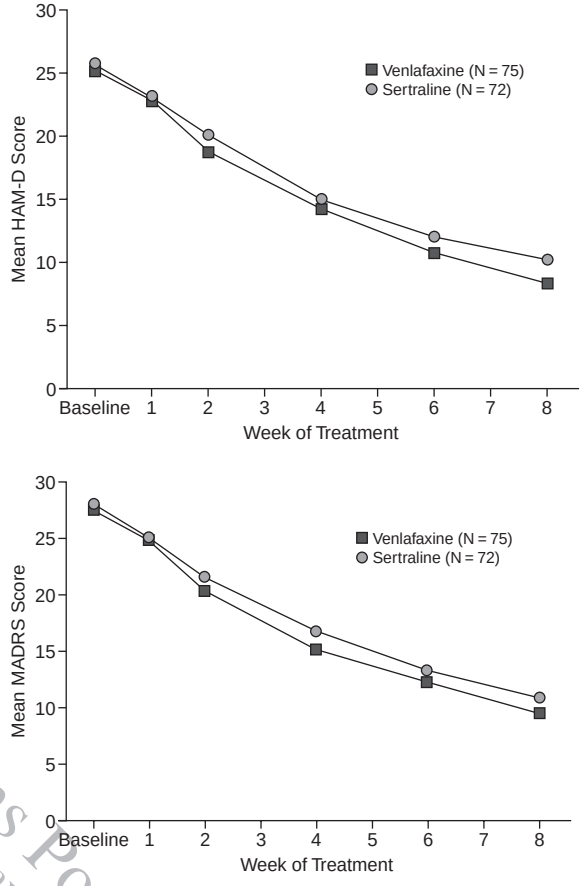
mon reasons were adverse event and unsatisfactory response/lack of efficacy. Eight of 16 patients on venlafaxine therapy and 3 of 12 on sertraline therapy discontinued during the first week; 6 taking venlafaxine and 1 taking sertraline discontinued for adverse events (not significant).

Efficacy

Significant ($p < .05$) reductions from baseline to week 8 were recorded for mean HAM-D and MADRS scores in both venlafaxine and sertraline groups (Figure 1). No significant differences between groups were observed at any time point. Likewise, significant ($p < .05$) reductions from baseline to week 8 also were recorded for CGI-S scores, but no differences were noted between groups.

After 6 weeks of treatment, a response, i.e., a decrease of ≥ 50% on the HAM-D, was noted in 74% (45/61) of patients on venlafaxine therapy and 59% (38/65) on sertraline therapy ($p = .04$). This difference remained at week 8,

Figure 1. Mean HAM-D and MADRS Scores at Each Assessment[a]

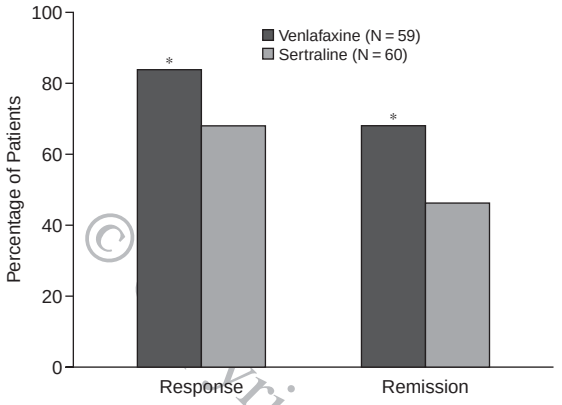


[a]Modified intent-to-treat analysis.

when 83% (49/59) of venlafaxine-treated and 68% (41/60) of sertraline-treated patients were considered responders ($p = .05$) (Figure 2). Likewise, significantly more patients in the venlafaxine group (68%; 40/59) than in the sertraline group (45%; 27/60) had a remission (HAM-D score < 10) at week 8 ($p = .008$) (Figure 2). No significant differences were noted in response rates on the MADRS ($p = .581$) and CGI ($p = .332$). The global response was 77% (47/61) with venlafaxine and 57% (37/65) with sertraline at week 6 ($p = .01$) and 81% (48/59) with venlafaxine and 75% (45/60) with sertraline at week 8 ($p = .430$). A sustained response was recorded in 70% (49/70) of patients with venlafaxine and 59% (41/69) with sertraline ($p = .184$).

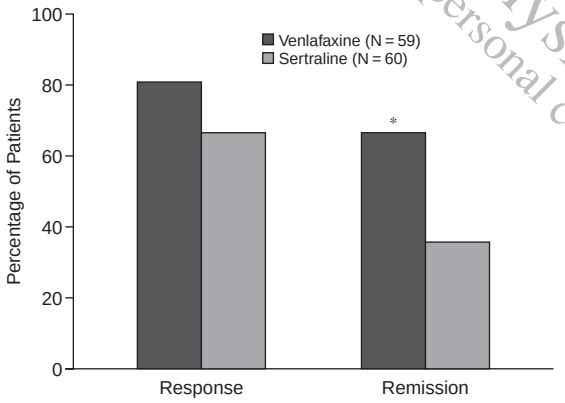
After the first 2 weeks of treatment, 39 patients (52%) taking venlafaxine and 46 (64%) taking sertraline increased their dose to 150 mg/day and 100 mg/day, respectively. The HAM-D response rate among patients who increased their dose was 81% (29/36) with venlafaxine and 67% (26/39) with sertraline (Figure 3). Moreover, the remission rate (HAM-D score < 10) among patients who in-

Figure 2. HAM-D Response Rate and Remission Rate at Week 8 With Venlafaxine and Sertraline[a]



[a]Response defined as ≥ 50% decrease from baseline in HAM-D score; remission defined as HAM-D score < 10.
*p ≤ .05 vs. sertraline.

Figure 3. HAM-D Response Rate and Remission Rate at Week 8 With Venlafaxine and Sertraline Among Patients Increasing Their Dose[a]



[a]Response defined as ≥ 50% decrease from baseline in HAM-D score; remission defined as HAM-D score < 10.
*p < .05 vs. sertraline.

creased their dose was 67% (24/36) with venlafaxine and 36% (14/39) with sertraline at week 8 ($p < .05$).

Before the trial, 15 venlafaxine-treated patients (20%) and 10 sertraline-treated patients (14%) were taking benzodiazepine derivatives. During the study, benzodiazepines were used for sleep in 19 (25%) of the venlafaxine group and 26 (36%) of the sertraline group.

Tolerability

The most common treatment-related adverse events with venlafaxine were nausea, headache, and sweating and with sertraline were nausea, headache, and diarrhea (Table 3). No significant differences were observed between treatment groups for adverse events. The most common adverse events causing discontinuation were nausea (N = 6; 8%) with venlafaxine and anxiety (N = 3; 4%) with sertraline. The mean change from baseline in diastolic blood pressure ranged from –0.1 to 2.1 mm Hg with venlafaxine and from –2.0 to –0.9 mm Hg with sertraline. No clinically relevant changes were noted in pulse, blood pressure, or weight with either venlafaxine or sertraline.

On the UKU, changes from baseline in the autonomic score (nausea, diarrhea, and sweating) decreased significantly ($p < .05$) during sertraline treatment, while changes in the psychic score (concentration, sleep, and tension) improved significantly ($p < .05$) during venlafaxine treatment (Table 4).

Table 3. Most Common Adverse Events (≥ 10% incidence)

	Venlafaxine (N = 75)		Sertraline (N = 72)	
Event	N	%	N	%
Diarrhea	6	8.0	10	13.9
Dizziness	10	13.3	5	6.9
Headache	21	28.0	21	29.2
Insomnia	9	12.0	8	11.1
Nausea	27	36.0	21	29.2
Sexual dysfunction[a]	6	8.0	4	5.6
Somnolence	5	6.7	8	11.1
Sweating	14	18.7	8	11.1
Tremor	8	10.7	7	9.7

[a]Includes increased or decreased libido, abnormal orgasm/ejaculation, anorgasmia, and impotence.

Table 4. Baseline and 8-Week Scores for the UKU Side Effect Rating Scale

	Venlafaxine (N = 59)		Sertraline (N = 60)	
UKU Scale	Mean	SD	Mean	SD
Psychic				
Baseline	5.7	1.7	5.6	1.6
8-week	2.3	1.7*	2.7	2.0
Neurologic				
Baseline	0.4	0.5	0.5	0.7
Final	0.1	0.3	0.2	0.4
Autonomic				
Baseline	1.2	1.5	1.3	1.5
8-week	0.7	0.7	0.6	1.0*
Sexual-male				
Baseline	1.8	2.0	2.0	2.1
8-week	1.9	1.6	1.3	1.7
Sexual-female				
Baseline	3.7	2.6	3.0	2.7
8-week	2.0	2.3	2.2	2.4
Headache				
Baseline	0.7	0.8	0.5	0.8
8-week	0.2	0.5	0.3	0.6

*p < .05 vs. baseline.

DISCUSSION

This is the first published double-blind, randomized study comparing venlafaxine and sertraline for the treatment of major depression. The results show that venlafax-

ine and sertraline were effective for the treatment of outpatients with major depression. However, venlafaxine was significantly more effective than sertraline in producing a response on the HAM-D at the doses compared. Further, venlafaxine induced a remission, defined by a HAM-D score less than 10, in significantly more patients than did sertraline. Among patients who increased their dose of venlafaxine (to 150 mg/day) or sertraline (to 100 mg/day), the remission rate was significantly higher with venlafaxine; approximately twice as many patients who increased their dose experienced a remission with venlafaxine.

These findings are consistent with results from previous double-blind, randomized trials in both depressed outpatients and hospitalized patients comparing venlafaxine with fluoxetine and paroxetine.[1–4] Previous studies have shown that venlafaxine, 75 mg/day, is as effective as fluoxetine or paroxetine, 20 mg/day,[7] and doses of 150 mg/day or more of venlafaxine are superior to higher doses of fluoxetine and paroxetine in depressed inpatients or outpatients.[1,2,4] In addition, results from placebo-controlled comparisons of venlafaxine extended release (XR) and fluoxetine demonstrate higher response or remission rates with venlafaxine XR.[17,18] The results from the present study confirm and extend these findings.

The rate of remission is a more clinically relevant endpoint than response. Remission represents the proportion of patients who have recovered or are well, whereas responders may still have residual symptoms of depression. The definition of a cutoff score for remission varies widely. Frank and colleagues[19] suggested using a 17-item HAM-D score of less than 7 to define remission. However, a survey of antidepressant trials found that HAM-D scores ranging from 5 to 15 were used to define remission.[20] Others have used a 17- or 21-item HAM-D score of 10 or less to define remission in clinical trials of paroxetine, fluoxetine, and reboxetine.[21–23] Marked differences have been noted between venlafaxine and selective serotonin reuptake inhibitors (SSRIs) when a remission criterion is used as the outcome measure.[2,4,18] The present results are consistent with the robust efficacy and dose-response effects of venlafaxine that may be attributed to its combined serotonin and norepinephrine activity.

The absence of a significant separation between treatment groups by mean scores on psychiatric rating scales in this trial is interesting. A similar finding was reported in a comparison of venlafaxine and paroxetine among patients not responding to previous SSRI treatment.[4] Those authors attributed the finding to a nonnormal distribution of raw scores compared with a dichotomous distribution for response and remission rates. Although the absence of significant separation in our trial could be attributed to the effects of an endpoint analysis used in our study, we found no evidence of a time × treatment interaction, although data were not analyzed for a nonnormal distribution.

The use of higher doses may have improved the outcome in the sertraline treatment group. The dosage range of 50 to 100 mg/day was selected to represent the usual dose of sertraline in clinical practice. Further, similar to other SSRIs, sertraline has been reported to demonstrate a flat dose-response curve.[10] In comparison, the dosage range of venlafaxine used in this trial (75–150 mg/day) also may have limited optimal effectiveness.

Over the entire duration of the study, tolerability was comparable between venlafaxine and sertraline. While the number of discontinuations was higher with venlafaxine, they occurred during the first week of therapy with no differences between groups thereafter. Nausea was the most common adverse event with both drugs, which is typically reported in other clinical trials.[3,24] No significant changes in blood pressure were noted with either drug.

Changes in the UKU scores revealed significant differences between venlafaxine and sertraline on the psychic and neurologic subscales. These findings are not unexpected, considering the pharmacologic and clinical profile of these drugs. Improvements in the UKU psychic scale score with venlafaxine are consistent with the greater antidepressant response noted at higher doses with traditional psychiatric rating scales.[2–4] The remaining effects of venlafaxine on the UKU autonomic scale likely represent an effect of norepinephrine, which is consistent with the known pharmacologic profile of venlafaxine.[25]

In summary, the results from this clinical trial suggest that venlafaxine is superior in efficacy to sertraline. In particular, the number of patients with remission both in the total group and among patients who increased their dose was significantly higher with venlafaxine. These results reinforce the positive dose response and efficacy of venlafaxine.

Drug names: fluoxetine (Prozac), oxazepam (Serax and others), paroxetine (Paxil), reboxetine (Vestra), sertraline (Zoloft), temazepam (Restoril and others), venlafaxine (Effexor).

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