

Randomized Trial of Sertraline Versus Venlafaxine XR in Major Depression: Efficacy and Discontinuation Symptoms

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Background: The comparative efficacy of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) was recently debated. Meta-analyses, based mainly on fluoxetine comparator data, suggest that the SNRI venlafaxine has superior efficacy to SSRIs in treatment of major depression.

Objective: To compare quality of life (QOL), efficacy, safety, and tolerability associated with sertraline and venlafaxine extended release (XR) for treatment of DSM-IV major depression.

Method: This was an 8-week, double-blind, randomized study of sertraline (50–150 mg/day) versus venlafaxine XR (75–225 mg/day), followed by a 2-week taper period. Subjects were recruited from 7 sites in Turkey and 6 sites in Australia between October 2002 and July 2003. The primary outcome measure was the Quality of Life Enjoyment and Satisfaction Questionnaire. Secondary outcome measures included measures of depression (including response and remission), anxiety, pain, safety (e.g., blood pressure), and tolerability (e.g., discontinuation symptoms).

Results: A total of 163 subjects received study treatment (women, 69%; mean age, 37.0 [SD = 12.9] years). No significant differences in QOL or efficacy were noted between treatments on the primary or secondary endpoints for the total study population or the anxious depression and severe depression subgroups. A priori analyses of symptoms associated with treatment discontinuation demonstrated no difference between treatment groups. However, in post hoc analyses, sertraline was associated with less burden of moderate to severe discontinuation symptoms. Venlafaxine XR was associated with a relative increase in mean blood pressure (supine diastolic blood pressure, –4.4 mm Hg difference at week 8/last observation carried forward).

Conclusion: Sertraline and venlafaxine XR demonstrated comparable effects on QOL and efficacy in treatment of major depression, although sertraline may be associated with a lower symptom burden during treatment discontinuation and a reduced risk of blood pressure increase.

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The comparative efficacy of selective serotonin reuptake inhibitor (SSRI) and serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressants was recently debated in publications based on meta-analyses.^{1,2} In addition to the limitations inherent in meta-analyses (being retrospective by definition and combining studies with different designs, populations, and periods of time³), the results of these studies are, by and large, based on comparisons of the SNRI venlafaxine with the SSRI fluoxetine. The majority of studies in these meta-analyses did not demonstrate differences between venlafaxine and an SSRI, and some of the placebo-controlled studies may be considered failed since 1 or more of the comparator antidepressants did not separate from placebo.

Only 2 published studies compared an SNRI (venlafaxine immediate release) to sertraline: Mehtonen et al.⁴ and Oslin et al.⁵ The primary measures in these studies did not demonstrate differences between sertraline and venlafaxine, but in the Oslin et al. study, venlafaxine was less well tolerated and was associated with more serious adverse events than sertraline. No studies have compared sertraline with venlafaxine extended release (XR).

There are some suggestions that SSRIs are not all equally effective. A recent combined analysis of studies of

sertraline versus fluoxetine⁶ suggested superiority of sertraline in a severe depression group, indicating that there may be differences in efficacy between SSRIs. Furthermore, clinical studies have compared the relative safety and tolerability between SNRIs and SSRIs, as well as among SSRIs. Early reports suggest important differences in safety and tolerability, specifically in the impact on blood pressure⁷ and adverse events associated with treatment discontinuation.^{8,9}

The current study was designed to test for differences between sertraline and venlafaxine XR in the treatment of major depressive disorder (MDD) using a quality of life (QOL) measure. A QOL assessment was chosen as the primary efficacy measure in this study due to its relevance to the dysfunction, management, compliance, and recovery associated with major depression and its treatment¹⁰⁻¹² and for providing a global assessment from the patient's point of view, a perspective that is rarely obtained in depression trials. In addition, QOL measures have been able to differentiate between depression treatments where all other efficacy measures failed; specifically, sertraline was associated with greater improvements in QOL in studies versus amitriptyline, nortriptyline, and imipramine.¹²⁻¹⁴ The current study also tested for differences in efficacy between the treatments using traditional measures of depressive symptomatology (e.g., response and remission rates) as well as differences in safety (e.g., blood pressure) and tolerability (e.g., discontinuation symptoms).

METHOD

Participants

Outpatients 18 years of age or older were included in this study if they had a 17-item Hamilton Rating Scale for Depression (HAM-D)¹⁵ total score of ≥ 18 at screening visit (with HAM-D item 1 [depressed mood] score ≥ 2) and met criteria for MDD, single episode or recurrent, without psychotic features as defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*.¹⁶ Diagnosis was made using the Mini-International Neuropsychiatric Interview (MINI) Version 5.0.0.¹⁷ Women of childbearing age had to have a negative serum β -hCG (β -human chorionic gonadotropin) pregnancy test and practice an effective form of contraception.

Potential subjects were excluded if they had a history of bipolar disorder, any psychotic disorder, delirium, dementia, alcohol/drug abuse/dependence (in the past 6 months), or schizoid, schizotypal, or borderline personality disorders. DSM-IV Axis I diagnoses not listed above were permitted only if they were identified as secondary diagnoses. Subjects were also excluded if they had a history of nonresponse to sertraline (at least 150 mg/day for 4 weeks or more), venlafaxine, or venlafaxine XR (at least 150 mg/day for 4 weeks or more) or nonresponse to an adequate trial of 2 antidepressants in the current episode.

This multicenter international study was conducted in 7 sites in Turkey and 6 sites in Australia and was conducted in compliance with Good Clinical Practice, including the International Conference on Harmonization (ICH) Guidelines¹⁸ consistent with the most recent version of the Declaration of Helsinki. The protocol was approved by each site's independent ethics committee, and all subjects provided written informed consent to participate in the study.

Interventions

This was an 8-week, double-blind (double-dummy design), randomized, parallel group study of flexibly titrated sertraline (50–150 mg/day) versus venlafaxine XR (75–225 mg/day) followed by a 2-week taper period. Dosage could be increased in increments of 50 mg for sertraline and 75 mg for venlafaxine XR at scheduled visits, at least 1 week apart, in the event that the subject did not exhibit a satisfactory treatment response and in the absence of dose-limiting side effects. Dose reductions of the same magnitude were allowed at weeks 2, 3, 4, and 6 to a minimum of 50 mg/day for sertraline or 75 mg/day for venlafaxine XR. Subjects were discontinued from the study if it was determined that they took less than 80% or more than 120% of allocated study drug between 2 consecutive visits.

Beginning at the week 8 visit, subjects were tapered off their double-blind medication at a rate not exceeding 50 mg/day for sertraline or 75 mg/day for venlafaxine XR every 4 days, with the goal of having all subjects study-drug-free by the end of week 10.

Objectives

The primary objective of the study was to test for differences between sertraline and venlafaxine XR on measures of QOL. The secondary objectives were to test for efficacy differences between both treatments on measures of depressive symptomatology (e.g., pain, response and remission rates), as well as differences in safety (e.g., blood pressure) and tolerability (e.g., discontinuation symptoms).

Efficacy Measures

The primary efficacy measure was the total score at week 8 (endpoint of acute treatment phase) on the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)–short form.¹¹ This scale was used to assess patients' perceived QOL and satisfaction across multiple domains. The Q-LES-Q is a self-administered 16-item scale used to measure a subject's perceived QOL across various domains of functional activity. The first 14 items assess domains such as social relationships, living or housing situation, and physical health. Item 15 is concerned with satisfaction with medication. Item 16 is a global rating of overall life satisfaction and contentment.

Each item was scored on a 5-point Likert scale (1 = very poor, 5 = very good) indicating the degree of enjoyment or satisfaction achieved during the past week. The first 15 items were summed to form a total score, which was converted to a percentage of the maximum total score. Higher scores represent greater life enjoyment and satisfaction. The Q-LES-Q was administered at every study visit.

Secondary efficacy measures administered at every study visit included the 17-item HAM-D, the Clinical Global Impressions-Severity of Illness scale (CGI-S), the Clinical Global Impressions-Improvement scale (CGI-I; at postbaseline visits),¹⁹ the Hamilton Rating Scale for Anxiety (HAM-A),²⁰ and visual analog scales (VAS) for depression and for overall assessment of pain.²¹ The VAS for pain was added halfway through the study, and hence only a small portion of subjects completed it. The Endicott Work Productivity Scale (EWPS)²² was administered at baseline and week 8.

Clinical assessments were performed by the same qualified rater at every visit whenever possible. If this was not possible, a rater with whom interrater reliability had been established completed the assessments. A qualified rater was defined as an M.D., Ph.D., or master's level clinician with previous experience performing the efficacy assessments used for this study.

Safety and Tolerability Assessments

The AntiDepressant Discontinuation Scale (ADDS) is a clinician-rated checklist that assesses the intensity (0–3 scale) of adverse events and the putative relationship of adverse events to discontinuation (1–4 scale). There are 30 signs and symptoms included on the checklist (see Appendix A). The ADDS also includes a global investigator assessment of discontinuation symptoms, which is a 6-point Likert scale (from 0 = none to 5 = very severe). The 30 signs and symptoms in the ADDS are: anxiety, chills, confusion, crying spells, diarrhea, difficulty concentrating, dizziness, drowsiness, faintness, fasciculations/myoclonus, fatigue, headache, hypomania, impaired coordination, insomnia, irritability, jitteriness, myalgia, nausea, paresthesia, rebound depression, sweating, tachycardia, tremor, unstable or rapidly changing mood, vertigo, vivid dreams, vomiting, weakness, and yawning. The ADDS was developed for this and related studies, as, to the authors' knowledge, no validated scales for assessment of discontinuation symptoms were available at the time of study design. See Appendix A for details of the ADDS.

In addition to recording all observed or volunteered adverse events during the study (regardless of suspected causal relationship to study drug), any sign or symptom that was elicited using the ADDS was also recorded as an adverse event.

Heart rate and blood pressure measurements (supine and standing, systolic and diastolic) were recorded at every study visit.

Sample Size

A sample size of 80 subjects per group was necessary in order to provide at least 80% power to detect a clinically meaningful difference of 5.8, with a standard deviation (SD) of 13 (at $\alpha = .05$ significance level), between sertraline and venlafaxine XR (intent-to-treat [ITT] analysis). The estimated SD and the difference judged to be clinically meaningful were based on prior studies that used the Q-LES-Q.¹²

Randomization

Subjects were randomly assigned to receive either sertraline or venlafaxine XR in a 1:1 ratio using a randomly permuted block method (with a block size of 4) stratified by center.

Statistical Methods

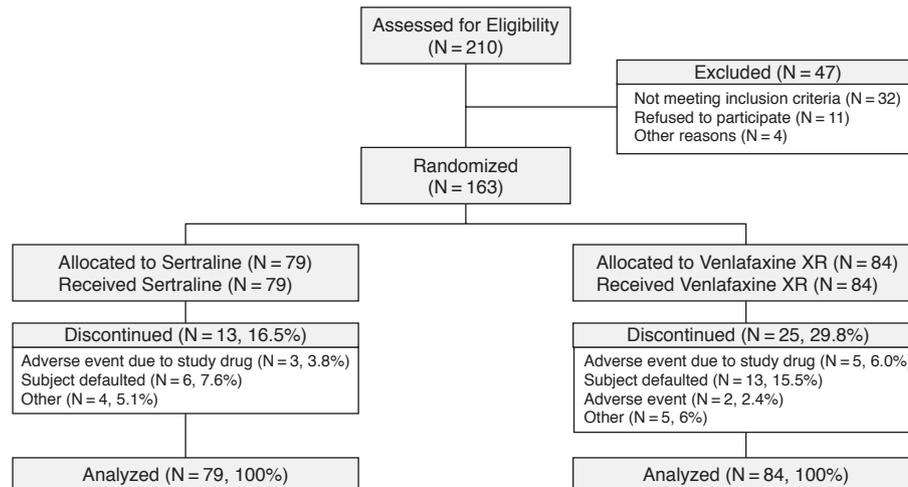
All subjects randomly assigned to treatment who received at least 1 dose of assigned study medication were eligible for inclusion in the ITT analysis population. Data that were missing at endpoint (week 8) were replaced using the last observation carried forward (LOCF). Baseline values were not carried forward. All statistical tests were 2-sided, with $p < .05$ considered significant for treatment differences. All analyses described below were prespecified unless otherwise indicated. The data were managed and analyzed centrally using the SAS version 8.2 software (SAS Institute, Cary, N.C.).

Differences between the treatment groups in change from baseline to endpoint (week 8/LOCF) for the primary outcome measure, Q-LES-Q score, and applicable secondary endpoints (HAM-D total score, HAM-A total score, VAS for depression score, VAS for pain score, and EWPS score) were tested using analysis of covariance (ANCOVA) with the baseline assessment fitted as the covariate and treatment and study site fitted as factors; least squares (LS) means from these models are presented.

Treatment differences measured by the CGI-I and CGI-S were tested at week 8/LOCF using a Cochran-Mantel-Haenszel (CMH) test for ordinal data stratified by site. The proportions (sertraline vs. venlafaxine XR) of CGI-I responders, HAM-D responders, and HAM-D remitters were compared at week 8/LOCF using a CMH test stratified by site. HAM-D response was defined as a $\geq 50\%$ reduction in total score, and remission was defined as a total score ≤ 7 . CGI-I response was defined as a rating of 1 (very much improved) or 2 (much improved).

The HAM-D analyses were repeated for 2 a priori-defined prespecified subgroups, an anxious depression subgroup (comprising subjects with a baseline HAM-D anxiety/somatization score ≥ 7 [defined as the sum of HAM-D items 10, 11, 12, 13, 15, and 17]) and a severe depression subgroup (comprising subjects with a baseline HAM-D total score ≥ 26 or CGI-S score ≥ 5).

Figure 1. Subject Flow



Abbreviation: XR = extended release.

Signs and symptoms reported in the ADDS at weeks 9 or 10 that were not present at week 8, or had increased in severity since week 8, were defined as discontinuation emergent. Incidence rates for these discontinuation-emergent signs and symptoms were calculated for each treatment group. Furthermore, deteriorations in individual signs and symptoms, from week 8 to worst severity recorded during taper, were summed to form a deterioration during taper period score. Treatment differences on this score were tested using analysis of variance, with treatment and study site fitted as factors.

A CMH test for ordinal data stratified by site was used to test for differences between treatment groups on the most severe rating obtained on the investigator assessment of discontinuation symptoms over the taper period.

The median time to termination of taper was estimated using the Kaplan-Meier method. A log-rank test was performed to test for treatment differences.

The following post hoc analyses were performed: Fisher exact tests were applied to (1) discontinuation-emergent symptoms with an incidence rate that differed between the treatment groups by > 10%; (2) discontinuation-emergent symptoms that were of at least moderate intensity with a 2-fold or greater difference in incidence rate between the treatment groups; and (3) discontinuation rates. Changes in blood pressure and heart rate from baseline to week 8 were analyzed post hoc using ANCOVA with the baseline assessment fitted as the covariate and treatment and study site fitted as factors. Adverse events that had an incidence > 20% were tabulated for the purpose of this report. The efficacy, blood pressure, and heart rate analyses were repeated post hoc for subjects who completed the 8-week acute treatment period.

RESULTS

Recruitment

Subjects were recruited from 7 sites in Turkey and 6 sites in Australia between October 2002 and July 2003. The last subject's last visit was in September 2003.

Subject Flow

A total of 210 subjects were screened, and 163 were randomly assigned to and received study drug (Figure 1). Of the 79 and 84 subjects that were treated with sertraline and venlafaxine XR, 66 (83.5%) and 59 (70.2%) completed the acute treatment phase of the study and entered the discontinuation phase, respectively.

Baseline Data

Demographic and clinical baseline characteristics were similar for both treatment groups (Table 1). Sixty-nine percent of subjects were women, and the mean age was 37.0 (SD = 12.9) years. For approximately half of the subjects in each group, this was the first single major depressive episode they had experienced (46.8%, sertraline; 47.6%, venlafaxine XR). Family history of affective disorder was 53.2% and 40.5% in the sertraline and venlafaxine XR groups, respectively, and family history of alcohol/drug abuse or dependence was 19.0% and 20.2%, respectively.

Numbers Analyzed

All randomized subjects received at least 1 dose of study medication (sertraline, N = 79; venlafaxine XR, N = 84); however, some subjects had no postbaseline data available for inclusion in certain analyses. The number of subjects contributing to each analysis is shown in the results tables.

Table 1. Demographic and Clinical Baseline Characteristics of MDD Outpatients (N = 163) Randomly Assigned to Treatment With Sertraline Versus Venlafaxine XR^a

Characteristic	Sertraline (N = 79)	Venlafaxine XR (N = 84)
Sex, female	57 (72.2)	56 (66.7)
Age, mean \pm SD, y	37.3 \pm 13.5	36.8 \pm 12.4
White	76 (96.2)	84 (100)
First single MDE	37 (46.8)	40 (47.6)
College grad or higher	15 (19.0)	18 (21.4)
Married	46 (58.2)	45 (53.6)
Employed	34 (43.0)	35 (41.7)
Family member diagnosis		
Affective disorder	42 (53.2)	34 (40.5)
Alcohol/drug abuse or dependence	15 (19.0)	17 (20.2)
Q-LES-Q total score, mean \pm SD	55.3 \pm 9.4	52.7 \pm 11.2
HAM-D total score, mean \pm SD	23.4 \pm 4.4	23.5 \pm 4.4
CGI-S score, mean \pm SD	4.5 \pm 0.8	4.6 \pm 0.8

^aData are presented as N (%) unless otherwise indicated. Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D = Hamilton Rating Scale for Depression, MDD = major depressive disorder, MDE = major depressive episode, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire, XR = extended release.

Outcomes

For the total subject group there were no statistically significant differences on any of the primary or secondary outcomes, and both treatments produced comparable efficacy results (Table 2). On the primary outcome, Q-LES-Q, an improvement of (LS mean \pm SE) 16.8 \pm 1.77 for sertraline and 17.5 \pm 1.79 for venlafaxine XR was observed at week 8/LOCF (difference = -0.7; 95% CI = -5.1 to 3.7; $p = .74$). On the HAM-D, a decrease (i.e., improvement) of -15.9 \pm 0.95 for sertraline and -14.3 \pm 0.94 for venlafaxine XR was observed at week 8/LOCF (difference = -1.6; 95% CI = -4.0 to 0.7; $p = .17$). HAM-D response and remission rates were relatively high and comparable in both treatment groups (Table 2).

Subgroup Analyses

Anxious depression subgroup. There were no statistically significant differences in efficacy between treatment groups in the a priori–defined anxious depression subgroup. This subgroup, defined by a baseline HAM-D anxiety/somatization subscale score ≥ 7 , comprised approximately 3 quarters of the total subject population at baseline (73.6% [120/163] for the total group; sertraline, 68.4% [54/79]; venlafaxine XR, 78.6% [66/84]). Improvement on the HAM-D total score at week 8/LOCF was 17.3 \pm 1.06 for sertraline and 14.8 \pm 1.02 for venlafaxine XR (difference = -2.5; 95% CI = -5.2 to 0.2; $p = .070$). HAM-D response (sertraline, 79.6%; venlafaxine XR, 68.9%; $p = .26$) and remission (sertraline, 63.0%; venlafaxine XR, 54.1%; $p = .44$) rates were relatively high and comparable in both treatment groups. Response on the HAM-D anxiety/somatization subscale was also high for this subgroup but nonsignificant between treatments (sertraline, 83.3%; venlafaxine XR, 70.5%; $p = .12$).

Severe depression subgroup. Subjects with severe depression, defined as baseline HAM-D total score ≥ 26 or a baseline CGI-S score ≥ 5 , made up approximately half of the total subject population at baseline (51.5% [84/163] for the total group; sertraline, 48.1% [38/79]; venlafaxine XR, 54.8% [46/84]). In this subgroup, improvement on the HAM-D total score at week 8/LOCF was 17.8 \pm 1.66 for subjects treated with sertraline and 15.4 \pm 1.60 for subjects treated with venlafaxine XR (difference = -2.3; 95% CI = -6.2 to 1.5; $p = .24$). HAM-D response (sertraline, 71.1%; venlafaxine XR, 71.4%; $p = .82$) and remission (sertraline, 63.2%; venlafaxine XR, 52.4%; $p = .27$) rates were relatively high and comparable in both treatment groups.

Safety and Tolerability

Mean dose at week 8 was 105.4 \pm 29.51 mg/day for sertraline (N = 69) and 161.4 \pm 44.36 mg/day for venlafaxine XR (N = 62). During the first calendar week of treatment there were 3 discontinuations in the sertraline group and 13 in the venlafaxine XR group ($p = .016$). Five of the discontinuations from the venlafaxine XR group during the first calendar week were determined to be related to study treatment. In the sertraline group, only 1 of the discontinuations due to treatment-related adverse events occurred in the first calendar week. For the entire study, discontinuations due to treatment-related adverse events were reported in 3.8% (3/79) of subjects in the sertraline group and 6.0% (5/84) in the venlafaxine XR group ($p = \text{nonsignificant}$). Treatment-related adverse events that had a frequency $> 20\%$ in either group over the entire study (i.e., including taper period) are reported in Table 3. Adverse event rates were found to be greater than those observed in previous studies of these drugs because adverse events were actively solicited during the taper period using the ADDS.

Signs and Symptoms of Discontinuation

There were no statistically significant differences between treatments for (1) the deterioration during taper period score; (2) the most severe rating obtained on the investigator assessment of discontinuation symptoms; or (3) time to termination of taper (median time of 4 days for both groups; $p = .91$). Table 4 shows 4 discontinuation-emergent symptoms that had a frequency of $> 10\%$ in the venlafaxine XR group compared with the sertraline group (dizziness, fatigue, vertigo, vivid dreams). There were no ADDS symptoms that had a frequency of $> 10\%$ with sertraline treatment compared with venlafaxine XR.

There were 8 discontinuation-emergent symptoms of at least moderate intensity that were more than twice as common in the venlafaxine XR group compared with the sertraline group (Table 4). There was only 1 discontinuation-emergent symptom of at least moderate intensity that was more than twice as common in the sertraline group than in the venlafaxine XR group.

Table 2. Primary and Secondary Efficacy Results at Week 8/LOCF for the Total Population

Measure	Sertraline		Venlafaxine XR		p Value
	Value	N	Value	N	
Q-LES-Q					
Total score, mean \pm SD	70.1 \pm 14.2	79	70.1 \pm 14.5	78	
Change ^a	16.8 \pm 1.77	79	17.5 \pm 1.79	77	.74
HAM-D					
Change ^a	-15.9 \pm 0.95	79	-14.3 \pm 0.94	79	.17
Response, %	70.9	56/79	70.9	56/79	.95
Remission, %	59.5	47/79	54.4	43/79	.47
HAM-A ^a	-14.1 \pm 0.99	79	-12.9 \pm 0.99	77	.32
VAS Depression ^a	-45.1 \pm 3.13	73	-42.0 \pm 3.00	76	.43
VAS Pain ^{a,b}	-20.7 \pm 6.18	13	-23.6 \pm 4.66	15	.67
EWPS ^a	-22.0 \pm 2.97	30	-17.9 \pm 3.08	29	.31
CGI-S score, mean \pm SD	2.0 \pm 1.10	79	2.2 \pm 1.25	81	.45
CGI-I score, mean \pm SD	2.0 \pm 1.22	79	2.1 \pm 1.35	81	.92
CGI-I response, %	73.4	58/79	69.1	56/81	.41

^aLeast squares mean change from baseline score \pm SE.

^bThe VAS for pain was added halfway through the study, hence the small numbers in this analysis.

Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, EWPS = Endicott Work Productivity Scale, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, LOCF = last observation carried forward, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire, VAS = visual analog scale, XR = extended release.

Effects on Heart Rate and Blood Pressure

There were statistically significant differences between both treatments in their effect on heart rate and blood pressure. For supine and standing heart rate, the changes from baseline to week 8/LOCF (LS mean \pm SE) for sertraline and venlafaxine XR were as follows: supine, 0.9 \pm 1.1 and 4.3 \pm 1.1 (difference = -3.3; 95% CI = -5.9 to -0.7; p = .013) and standing, 0.4 \pm 1.2 and 4.1 \pm 1.1 (difference = -3.7; 95% CI = -6.6 to -0.9; p = .01), respectively.

For systolic blood pressure, the changes from baseline to week 8/LOCF (LS mean \pm SE) for sertraline and venlafaxine XR were: supine, -3.0 \pm 1.43 and 0.8 \pm 1.41 (difference = -3.7; 95% CI = -7.3 to -0.2; p = .037) and standing, -0.8 \pm 1.67 and 0.6 \pm 1.65 (difference = 1.5; 95% CI = -5.6 to 2.6; p = .48), respectively. For diastolic blood pressure, the changes from baseline for sertraline and venlafaxine XR were: supine, -1.4 \pm 1.23 and 3.1 \pm 1.22 (difference = -4.4; 95% CI = -7.5 to -1.4; p = .004) and standing, -0.5 \pm 1.30 and 2.6 \pm 1.27 (difference = -3.1; 95% CI = -6.3 to 0.1; p = .056), respectively.

Week 8 Completer Analyses

The efficacy, blood pressure, and heart rate analyses were repeated for subjects who had completed the 8-week acute treatment period. The results of these analyses were consistent with those that were undertaken using the ITT principle on the week 8/LOCF data.

DISCUSSION

In this first randomized, double-blind study comparing sertraline with venlafaxine XR, no significant differences in efficacy were noted between the 2 treatments for the to-

tal study population, the anxious depression subgroup, or the severe depression subgroup, nor were they found on any of the efficacy measures tested, including measures of QOL, depressive symptomatology (including response and remission rates), anxiety, pain, work productivity, and global measures of clinical severity and improvement.

The study was adequately powered to reliably detect a clinically meaningful difference on the Q-LES-Q at week 8/LOCF of 5.8 points. The 95% CI for the estimated treatment differences on this week 8/LOCF ranged from -5.1 to 3.7. This result indicates that it is implausible that a clinically important difference of at least 5.8 points on Q-LES-Q exists between the treatments as administered per this protocol. Quality of life measurements have been shown to differentiate between antidepressant treatments when efficacy measures fail to show a difference. Specifically, sertraline treatment was found to be associated with greater improvements in QOL as measured by the Q-LES-Q compared with amitriptyline, nortriptyline, and imipramine.¹²⁻¹⁴ Findings from this study do not support superiority in efficacy of either treatment over the other.

Both sertraline and venlafaxine XR were generally well tolerated with only 3.8% (3/79) of sertraline-treated subjects and 6.0% (5/84) of venlafaxine XR-treated subjects discontinuing the study due to treatment-related adverse events. Differences between the treatments in measures of discontinuation symptoms during the taper period, heart rate and blood pressure measurements during the acute treatment phase, and dropouts within the venlafaxine XR group during the first calendar week of treatment were detected. However, these differences should not be considered conclusive as the results are based on post hoc analysis with no adjustment made for multiple comparisons.

Table 3. Treatment-Related Adverse Events (> 20% in either group) During the Entire Study (including taper period)^a

Adverse Event	Sertraline (N = 79)	Venlafaxine XR (N = 84)
Asthenia	21 (26.6)	21 (25.6)
Headache	35 (44.3)	27 (32.1)
Dry mouth	32 (40.5)	20 (23.8)
Nausea	41 (51.9)	40 (47.6)
Dizziness	26 (32.9)	22 (26.2)
Insomnia	28 (35.4)	23 (27.4)
Somnolence	17 (21.5)	22 (26.2)
Yawning	24 (30.4)	24 (28.6)
Sweating	25 (31.6)	18 (21.4)

^aData are presented as N (%).

Abbreviation: XR = extended release.

The current study is, to our knowledge, the first to assess the comparative effect of an SSRI and an SNRI on symptoms occurring during treatment discontinuation. In fact, to the authors' knowledge, no previously validated scales for assessment of discontinuation symptoms were available at the time of study design. Further studies to validate the instrument (the ADDS) developed for this purpose and its scoring system are required. The a priori analysis of the discontinuation symptom findings revealed no statistically significant differences between treatments during the taper period. However, post hoc analyses of discontinuation symptoms that were of moderate or greater severity suggested sertraline was associated with a lower burden of discontinuation symptoms compared with venlafaxine XR. This finding is consistent with early reports suggesting the possibility of a clinically relevant discontinuation syndrome with venlafaxine XR⁹ and a relatively benign one with sertraline.⁸ Discontinuation symptoms represent an important aspect of the clinical effectiveness of antidepressant drugs. Since a substantial minority of patients do not respond to a trial of antidepressant pharmacotherapy,²³ the need to discontinue treatment and switch to another treatment, and hence the possible occurrence of discontinuation symptoms, can be expected to be encountered regularly in the management of depression in clinical practice.

There was also some evidence suggesting differences between treatments in their effect on heart rate and blood pressure. Sertraline was generally associated with a marginal reduction in blood pressure, while venlafaxine XR was associated with a more pronounced increase in blood pressure. These results are consistent with earlier reports of blood pressure increases associated with venlafaxine treatment.⁷ Considering that major depression is a chronic illness with lifelong treatment recommended for patients having 3 or more episodes,^{24,25} long-term effects of antidepressant treatment on blood pressure become an important consideration.

Previous reports on the relative efficacy of venlafaxine versus SSRIs (namely fluoxetine)^{1,2} provided data suggesting efficacy advantages for venlafaxine over fluoxetine.

Table 4. AntiDepressant Discontinuation Scale (ADDS) Results

ADDS Item	Sertraline	Venlafaxine XR	p Value
Discontinuation-emergent symptoms with > 10% difference in incidence rate between treatments, %			
Dizziness	33.3	43.8	.22
Fatigue	22.2	32.8	.18
Vertigo	5.6	17.2	.052
Vivid dreams	26.4	42.2	.069
Discontinuation-emergent symptoms that were of at least moderate intensity, with a greater than 2-fold difference in incidence rate between treatments, %			
Unstable or rapidly changing mood	6.9	14.1	.26
Tremor	2.8	12.5	.046
Vertigo	0	12.5	.002
Tachycardia	4.2	9.4	.31
Confusion	1.4	9.4	.051
Impaired coordination	0	7.8	.02
Chills	2.8	7.8	.25
Fasciculations/myoclonus	2.8	0	.50
Hypomania	0	1.6	.47
Deterioration during taper period			
Total score, least squares mean \pm SD	7.8 \pm 1.14	10.2 \pm 1.20	.12
N	72	64	
Worst severity of discontinuation symptoms (investigator global assessment)			
N	67	62	.117
None, %	17.9	11.3	
Minimal, %	23.9	17.7	
Mild, %	23.9	27.4	
Moderate, %	34.3	38.7	
Severe, %	0.0	3.2	
Very severe, %	0.0	1.6	

Abbreviation: XR = extended release.

These reports went further to suggest generalizability of their findings to all SSRIs, but there is a growing body of literature suggesting important differences among SSRIs on a number of efficacy, safety, and tolerability parameters. For example, a recent combined analysis of 5 sertraline versus fluoxetine comparator studies suggested greater efficacy for sertraline in the severe depression group.⁶

A few limitations of the current study are of note. The study did not include a placebo treatment group; therefore, the possibility that some of the treatment effects were due to placebo effect cannot be excluded (e.g., the high rates of response and remission noted with both treatments in this study). Furthermore, the study was adequately powered to detect a clinically meaningful difference only on the primary endpoint (Q-LES-Q). The results from the subgroup and secondary efficacy, safety, and tolerability analyses will need to be confirmed in subsequent prospective studies. Finally, long-term continuation studies are needed to compare efficacy, safety, and tolerability of antidepressants in this chronic, lifelong illness.

In summary, in this study, sertraline and venlafaxine XR demonstrated comparable efficacy in the treatment of

depression, although sertraline may be associated with lower symptom burden during treatment discontinuation and a reduced likelihood of blood pressure increase.

Drug names: fluoxetine (Prozac and others), imipramine (Tofranil and others), nortriptyline (Aventyl, Pamelor, and others), sertraline (Zoloft), venlafaxine (Effexor).

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Appendix A appears on page 1320.

Appendix A. The AntiDepressant Discontinuation Scale (ADDS)

ANTIDEPRESSANT DISCONTINUATION SCALE (ADDS)

Please place an appropriate number response in each box.

Catalogue of Symptoms	Intensity	Relationship to Discontinuation
	0 – Not present 1 – Mild 2 – Moderate 3 – Severe	1 – None/Remote 2 – Possible 3 – Probable 4 – Definite
Anxiety		
Chills		
Confusion		
Crying spells		
Diarrhoea		
Difficulty concentrating		
Dizziness		
Drowsiness		
Faintness		
Fasciculations/Myoclonus		
Fatigue		
Headache		
Hypomania		
Impaired coordination		
Insomnia		
Irritability		
Jitteriness		
Myalgia		
Nausea		
Paresthesia		
Rebound depression		
Sweating		
Tachycardia		
Tremor		
Unstable or rapidly changing mood		
Vertigo		
Vivid dreams		
Vomiting		
Weakness		
Yawning		

TOTAL INTENSITY

<p>INVESTIGATOR: Please estimate the severity of serotonin reuptake inhibitor discontinuation symptoms experienced by the subject over the taper phase.</p> <p>0 = None 1 = Minimal 2 = Mild (rate only if subject did NOT postpone taper) 3 = Moderate 4 = Severe (rate only if subject postponed taper) 5 = Very Severe</p> <p>RATING: <input style="width: 50px; height: 20px;" type="text"/></p>

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