A Randomized, Double-Blind, Active-Control Study of Sertraline Versus Venlafaxine XR in Major Depressive Disorder

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Objective: Sertraline may produce dual neurotransmitter effects similar to the serotonin-norepinephrine reuptake inhibitors (SNRIs); however, it has been tested against an SNRI in only 1 previous study, and never at an optimal dose. The objective of the current multisite study was to compare relatively higher doses of sertraline (i.e., 150 mg/day) and venlafaxine extended release (XR) (225 mg/day) in outpatients with major depressive disorder.

Method: Subjects with DSM-IV major depressive disorder were randomly assigned to 8 weeks of double-blind treatment with sertraline (N = 82) or venlafaxine XR (N = 78). The study ran from January 2002 through January 2003. The primary outcome measure was the Quality of Life Enjoyment and Satisfaction Questionnaire; secondary outcome variables included the 17-item Hamilton Rating Scale for Depression.

Results: Both treatments led to significant improvement in depressive symptoms and quality-of-life measures. No significant differences were noted between treatment groups for final scores on the primary or secondary measures. The treatment groups did not differ significantly in the percentage of responders (sertraline = 55%, venlafaxine XR = 65%; intent-to-treat [ITT] sample) or remitters (sertraline = 38%, venlafaxine XR = 49%; ITT sample), although the proportions are similar to those found in earlier selective serotonin reuptake inhibitor (SSRI) vs. venlafaxine meta-analyses. In patients who achieved the maximum dose of drug and maintained it for 3 weeks, response rates were similar to those found at lower doses (sertraline = 59%, venlafaxine XR = 70%); however, remission rates for this sample were comparable for both drug groups (sertraline = 48%, venlafaxine XR = 50%).

Conclusions: The efficacies of sertraline and venlafaxine XR were comparable. Although response and remission rates did not differ statistically, the rates were analogous to those reported in previous meta-analyses. However, at clinically relevant higher doses, the remission rates were very similar.

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Selective serotonin reuptake inhibitors (SSRIs) are among the most widely prescribed medications. However, soon after their introduction, concerns began to be expressed about their effectiveness relative to tricyclic antidepressants.[1–3] In contrast to the relative selectivity of SSRIs, most tricyclic antidepressants act by blocking the reuptake of both serotonin and norepinephrine. A difference in efficacy suggests that the combined mechanisms of action seen with tricyclic antidepressants may offer additional benefit beyond the specific mechanism of SSRI action.[3] This view has been supported by studies by Nelson et al.[4,5] showing that the combination of fluoxetine (an SSRI) and desipramine (a predominantly norepinephrine reuptake inhibitor) was superior to either drug given as monotherapy (although it should be noted that the later study showed differences on the Montgomery-Asberg Depression Rating Scale and not the Hamilton Rating Scale for Depression [HAM-D]). The implication, then, would be that drugs with combined serotonin and norepinephrine reuptake inhibition could have a stronger antidepressant effect than selective agents.

The antidepressant venlafaxine is a mixed serotonin and norepinephrine reuptake inhibitor[6] and, therefore, its action is thought to be similar to the tricyclics. The noradrenergic effect of venlafaxine has been demonstrated with a series of studies in humans, using the tyramine pressor test[7] and the papillary light reflex test,[8] although this effect seems to occur at doses of 150 mg/day or higher. A key question has been whether this combined action confers an enhanced level of therapeutic efficacy for venlafaxine extended release (XR). Thase et al.[9] conducted a pooled meta-analysis of 8 clinical trials comparing venlafaxine XR to SSRIs, including fluoxetine, paroxetine, and fluvoxamine. Although response rates (defined as a 50% reduction in HAM-D[10] score) did not differ, remission rates (HAM-D score ≤ 7) were significantly higher for venlafaxine XR (45% vs. 35%, odds ratio = 1.50). Another pooled meta-analysis comparing venlafaxine XR to SSRI or tricyclic antidepressant treatments concluded that venlafaxine XR produced significantly higher rates of response.[11] These findings have led some to conclude that combining serotonin and norepinephrine uptake inhibition enhances therapeutic efficacy relative to serotonin transporter antagonism alone.[12]

Sertraline is an antidepressant that has typically been considered an SSRI[13] and is a potent antagonist of the serotonin transporter, with low affinity for the norepinephrine transporter.[6] On the other hand, it represents the most potent inhibitor of the dopamine transporter among the currently available antidepressants (dissociation constant [K_d] ≈ 25 nanomolars [nM], serotonin/dopamine ratio ≈ 86).[14] Both laboratory[14–16] and human[17,18] studies suggest that sertraline may produce a clinically meaningful effect on dopamine reuptake, particularly at higher doses.[19] Additionally, because the dopaminergic system has been linked to motivation and reward processes,[19,20] treatment with sertraline might result in enhanced subjective well-being and life satisfaction for depressed patients compared to treatment with antidepressants without a direct dopaminergic effect. As an example, 1 study comparing sertraline and nortriptyline in older depressed patients found that while both drugs resulted in equivalent improvements in mood, sertraline produced greater improvements in quality-of-life domains.[21] A similar study in depressed adult outpatients likewise concluded that sertraline tended to produce greater improvement in quality-of-life measures compared with amitriptyline.[22]

Despite the frequency of comparisons between SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) in the literature, few studies have compared sertraline and venlafaxine. Thase et al.[9] did not include any studies of sertraline in their meta-analysis, while Einarson et al.[11] included a single study involving sertraline out of the 44 in their meta-analysis. One study that directly compared venlafaxine XR and sertraline concluded that venlafaxine XR resulted in a significantly greater proportion of responders and remitters (defined as HAM-D score < 10), although the mean termination HAM-D scores did not differ between groups.[23]

An important but often neglected issue in these types of analyses is dosage equivalency. For instance, Thase et al.[9] stated that "there is no evidence that venlafaxine XR is more effective than the SSRIs at minimum therapeutic doses."[9(p239)] However, what remains unclear is whether trials of venlafaxine XR against other medications that utilized comparable optimized doses would yield different results. For both venlafaxine XR and sertraline, higher doses are putatively associated with an increased range of neurotransmitter effects. Thus, it would be vital to make sure that these medications are tested at comparable doses before drawing conclusions about efficacy or range of effect.

A final issue of interest is the relationship between medication, depressive symptoms, and quality-of-life measures. As mentioned, comparative studies have suggested that, in the absence of differential improvements in depressive symptoms, sertraline treatment improves quality-of-life measures more than some tricyclic antidepressants. A recent study found that before treatment, depressive symptoms may not account for much variance in quality of life,[24] which led to a conclusion that quality of life and depression may be independent constructs with discrete reactions to treatments. If this is the case, it would be important to include both types of assessments in studies of depression.[25] Before drawing conclusions, however, it would be useful to investigate the relation of quality of life to depression symptoms, both pretreatment (when there may be statistical constraints on the size of any correlations due to restriction of range) and posttreatment (where a wider variance in scores may produce different results).

The objectives of the current study were to compare the efficacy, safety, and tolerability of relatively higher doses of sertraline (i.e., 150 mg/day) and venlafaxine XR (225 mg/day) in outpatients with major depressive disorder. The primary outcome measure was the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)[26]; secondary outcome variables included the 17-item HAM-D (HAM-D_{17}).[10,27] Our primary hypotheses were (1) that higher doses of sertraline would result in greater improvement in quality of life than would higher doses of venlafaxine XR; (2) that optimized doses of venlafaxine XR and sertraline would produce similar rates of response and remission and similar final mean HAM-D_{17} scores; and (3) that changes in quality-of-life measures would be inversely correlated with changes in depressive ratings.

METHOD

The study was conducted from January 2002 through January 2003 at 8 U.S. sites. The research protocol was

approved by local institutional review boards, and written informed consent was obtained from all subjects prior to any research activity.

Subjects

Participants were male and female outpatients aged 18 or older who met diagnostic criteria for major depressive disorder, single episode or recurrent, without psychotic features, according to *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV)[28] criteria. Diagnosis was established using the Structured Clinical Interview for DSM-IV.[29] Comorbid Axis I and Axis II disorders were allowed as long as major depressive disorder was the primary (i.e., clinically predominant) diagnosis, except as noted below. In addition, patients had to score ≥ 18 on the HAM-D_{17}[10,27] and ≥ 2 on item 1 (depressed mood).

Exclusion criteria included the following: current or past diagnosis of bipolar disorder or any psychotic disorder; current diagnosis of delirium or dementia; alcohol or drug abuse or dependence in the past 6 months (excluding nicotine and caffeine abuse/dependence); schizoid, schizotypal, or borderline personality disorder; previous nonresponse to sertraline (at least 50 mg/day for 4 weeks or more), to venlafaxine XR (at least 75 mg/day for 4 weeks or more), or to 2 antidepressants in the current episode; use of an antidepressant within 2 weeks of baseline (4 weeks for fluoxetine); use of herbal and/or homeopathic remedies within 2 weeks of baseline (excluding vitamin and mineral supplements); the use of any psychotropics within 1 week of baseline, with the exception of zolpidem or zopiclone as needed for sleep; the use of benzodiazepines taken on a regular, daily basis within 4 weeks of baseline (limited, as-needed use was allowed until 1 week prior to randomization); a score of 3 or 4 on the suicide item (item 3) of the HAM-D_{17} scale at screen visit or a score of 4 at baseline visit; participation in any other studies involving investigational or marketed products, concomitantly or within 90 days prior to entry into the study; treatment with monoamine oxidase inhibitors, including selegiline, within 14 days of baseline evaluation; treatment with electroconvulsive therapy within 30 days of baseline evaluation; a history of intolerance or hypersensitivity to sertraline and/or venlafaxine XR; the likelihood of requiring treatment during the study period with drugs not permitted by the study protocol; the presence of any serious and/or unstable medical condition; abnormal baseline laboratory findings considered by the investigator to be indicative of conditions that might affect study results; impaired hepatic function, as shown by but not limited to serum glutamic-pyruvic transaminase (alanine aminotransferase) (SGPT [ALAT]) or serum glutamic-oxaloacetic transaminase (aspartate aminotransferase) (SGOT [ASAT]) > 2 × the upper limit of normal; impaired renal function, as shown by but not limited to serum creatinine > 2.5 mg/dL; women with a positive pregnancy test or who were nursing; history of seizure disorder, excluding febrile seizures of childhood; a mental condition rendering the subject unable to understand the nature, scope, and possible consequences of the study; or evidence of nonadherence to the study procedures.

All participants received a physical exam, an electrocardiogram, and laboratory tests (including complete blood count, chemistries, thyroid function tests, urine drug screen, and urine pregnancy test for women).

Procedures

Persons who qualified were randomly assigned (1:1) to 8 weeks of double-blind treatment with either sertraline or venlafaxine XR. Drug was dispensed in identical capsules containing either 50 mg of sertraline or 75 mg of venlafaxine XR, dosed from 1–3 capsules per day. Dosing was flexible, but the investigators were encouraged to try to achieve the maximum dose of medication as tolerated (3 blinded capsules). Adherence to the dosing schedule was established using pill counts at each study visit. After completion of the study, medication was tapered over 1–5 days as tolerated. At the completion of the study or at early termination, all patients were referred to appropriate follow-up care.

Study visits included screening, baseline (within 1 week), and weeks 1, 2, 3, 4, 6, 8 (end of active treatment), and 10 (posttaper). Outcome measures included the HAM-D_{17},[10] the Q-LES-Q,[26] and the Clinical Global Impressions-Severity of Illness (CGI-S)[30] scale, obtained at all visits, and the Clinical Global Impressions-Improvement (CGI-I)[30] scale and the Hamilton Rating Scale for Anxiety (HAM-A),[31] assessed at baseline and subsequent visits. Vital signs were obtained at all visits. Adverse events were assessed by spontaneous patient report and by use of the Treatment Emergent Symptom Scale,[32] a clinician-administered list of symptoms that also allows assessment of symptoms emerging after taper from medication. All week-8 assessments were obtained in the event of early termination.

Data Analysis

Three sets of patient data were analyzed: (1) the intent-to-treat (ITT) evaluable population included all subjects randomly assigned to treatment who had no major protocol violations and who were at least 80% adherent on double-blind study medication for at least 2 weeks; the endpoint was the last observation carried forward; (2) the completer (COMP) sample, patients who completed all visits through week 8; and (3) patients who completed all visits and for at least the last 3 visits were taking 3 capsules of their assigned medication, i.e., 150 mg of sertraline or 225 mg of venlafaxine XR (END-3). The latter analyses were conducted in order to examine the impact of higher dosing levels.

Table 1. Baseline Demographics and Clinical Characteristics of Sample

Characteristic	Total Sample (N = 160)	Sertraline (N = 82)	Venlafaxine XR (N = 78)	Between-Group Comparison
Gender, %				
Male	47	54	39	NS
Female	53	46	61	
Race, %				
White	83	83	84	NS
African American	5	2	8	
Asian	3	5	1	
Other	9	10	7	
Age, mean (SD), y	39.3 (11.9)	41.2 (12.0)	37.2 (11.6)	t = 2.1, df = 158, p < .05
Depression diagnosis, %				
Single episode	49	49	48	NS
Recurrent	51	51	52	
Length of current episode, mean (SD), wk	59.7 (123.7)	60.4 (135.0)	58.9 (111.1)	NS
Q-LES-Q score, mean (SD)[a]	0.52 (0.09)	0.53 (0.10)	0.51 (0.08)	NS
HAM-D_{17} score, mean (SD)	22.3 (2.9)	22.1 (2.9)	22.4 (2.9)	NS
CGI-S score, % mildly ill	3	5	1	NS
CGI-S score, mean (SD)	4.2 (0.5)	4.1 (0.5)	4.2 (0.5)	NS
HAM-A score, mean (SD)	15.9 (4.8)	15.7 (5.1)	16.0 (4.4)	NS

[a]Expressed as a proportion of the total possible score of 70.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D_{17} = 17-item Hamilton Rating Scale for Depression, NS = not significant, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire, XR = extended release.

The primary analysis was the change from baseline to endpoint in the Q-LES-Q total score, conducted using analysis of covariance models including treatment and center as main effects and including baseline Q-LES-Q and age (the treatment groups differed significantly in age, as reported below) as covariates. The secondary analyses were changes from baseline to endpoint on the secondary efficacy parameters (HAM-D_{17}, CGI-S, CGI-I, HAM-A), using analysis of covariance models including treatment and center as main effects and including baseline scores and age as covariates.

In order to examine the relation of the Q-LES-Q and the HAM-D_{17} both at baseline and at end of treatment, we used methods consistent with Rapaport et al.[24] Stepwise linear regression analyses with duration of illness, age, anxiety comorbidity, sex, and HAM-D_{17} score as predictor variables were conducted separately for the baseline and week-8 Q-LES-Q scores.

Response was defined as the achievement of a 1 (very much improved) or 2 (much improved) on the CGI-I scale or a ≥ 50% reduction in HAM-D_{17} total score. Remission was defined as having a 1 or 2 on the CGI-I scale and ≤ 7 on the HAM-D_{17}. Groups were compared on rates of response and remission using the Cochran-Mantel-Haenszel general association statistic with centers as strata. Finally, the incidence of adverse events was compared using the χ^2 test (and Fisher exact test [2-tailed] where appropriate). All significance levels were 2-tailed and were set at the .05 level. The study had a power of 0.96 to detect a difference of 0.07 between groups on the primary outcome statistic, the Q-LES-Q.

RESULTS

A total of 160 patients were randomly assigned to sertraline (N = 82) or venlafaxine XR (N = 78). The intake sample characteristics are listed in Table 1. There were no statistically significant differences at baseline between groups except for age; the sertraline group was significantly older (t = 2.1, df = 158, p < .05). Age was included as a covariate in the primary and secondary analyses.

Two patients withdrew consent immediately after being randomly assigned, so the ITT sample consisted of 158 patients (82 in sertraline, 76 in venlafaxine XR). The COMP sample consisted of 130 patients (63 in sertraline, 67 in venlafaxine XR), and the END-3 sample consisted of 90 patients (46 in sertraline, 44 in venlafaxine XR). Nineteen (23%) of the sertraline patients dropped out of the study before the final week-8 visit, as did 11 (14%) of the venlafaxine XR patients (χ^2 = not significant [NS]). The rates of adverse event–related dropout did not differ by group; 1 of the sertraline patients and 3 of the venlafaxine XR patients discontinued the study because of side effects. The proportion of subjects achieving the maximum dose of 3 capsules for at least 1 visit did not differ by group (86% of the sertraline group and 85% of the venlafaxine XR group).

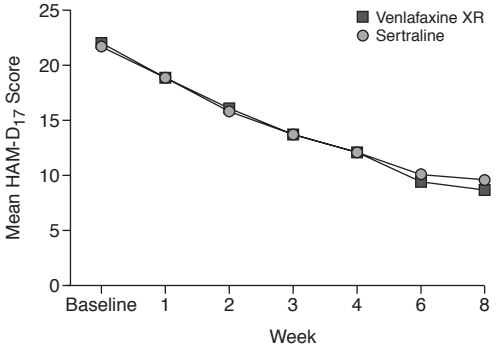
There were no statistically significant differences between the sertraline and venlafaxine XR groups on any outcome measure by any sample definition. Means and standard deviations for the primary and secondary outcome measures are listed in Table 2, as are rates of response and remission (defined by HAM-D_{17} scores).

Table 2. Endpoint Scores and Response and Remission Rates for Primary and Secondary Outcome Measures[a]

Measure	Sample	Sertraline	Venlafaxine XR
Q-LES-Q score, mean (SD)	ITT	0.69 (0.12)	0.67 (0.12)
	COMP	0.70 (0.12)	0.69 (0.11)
	END-3	0.68 (0.11)	0.68 (0.11)
$HAM\text{-}D_{17}$ score, mean (SD)	ITT	10.8 (6.4)	9.7 (6.4)
	COMP	9.6 (6.2)	8.4 (5.4)
	END-3	9.5 (5.7)	8.6 (4.8)
$HAM\text{-}D_{17}$ response rate, % (N/N)	ITT	55 (45/82)	65 (49/76)
	COMP	62 (39/63)	72 (48/67)
	END-3	59 (27/46)	70 (31/44)
$HAM\text{-}D_{17}$ remission rate, % (N/N)	ITT	38 (31/82)	49 (37/76)
	COMP	46 (29/63)	55 (37/67)
	END-3	48 (22/46)	50 (22/44)
CGI-S score, mean (SD)	ITT	2.6 (1.1)	2.4 (1.1)
	COMP	2.4 (1.1)	2.2 (0.9)
	END-3	2.4 (1.1)	2.3 (0.8)
CGI-I score, mean (SD)	ITT	2.3 (1.1)	2.0 (1.1)
	COMP	2.1 (1.1)	1.8 (0.9)
	END-3	2.0 (1.0)	1.8 (0.7)
HAM-A score, mean (SD)	ITT	9.1 (5.4)	8.2 (5.7)
	COMP	8.4 (5.3)	7.2 (5.0)
	END-3	7.9 (4.7)	7.3 (4.5)

[a]No significant group differences on any measure for any sample.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, COMP = completers, END-3 = completers who for at least the last 3 visits were taking 3 capsules of their assigned medication, HAM-A = Hamilton Rating Scale for Anxiety, $HAM\text{-}D_{17}$ = 17-item Hamilton Rating Scale for Depression, ITT = intent to treat, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire, XR = extended release.

Figure 1. Mean $HAM\text{-}D_{17}$ Score at Each Visit by Group



Abbreviations: $HAM\text{-}D_{17}$ = 17-item Hamilton Rating Scale for Depression, XR = extended release.

Scores on the primary outcome variable, the Q-LES-Q, did not differ significantly between groups. Significant improvements in individual domains as well as in the total score were demonstrated in both treatment groups. At the final visit, the mean total Q-LES-Q score (expressed as a proportion of the total score possible) for the sertraline group was 0.69 (SD = 0.12), and for the venlafaxine XR group, 0.67 (SD = 0.12) ($F = 0.05$, $df = 1,142$; $p = NS$). Both groups improved by 16% from intake. Scores were similar in the COMP and END-3 samples.

Q-LES-Q scores were analyzed separately in the venlafaxine XR and sertraline groups in patients who achieved therapeutic remission (ITT sample). The sertraline group showed a trend for greater improvement than venlafaxine XR on Q-LES-Q total score (sertraline = 0.77 [SD = 0.09]; venlafaxine XR = 0.73 [SD = 0.09]; $F = 3.48$, $df = 1,67$; $p = .07$).

Significant reductions in depressive symptoms from baseline to the final visit were noted in both groups (Figure 1), but there were no significant main effects for either group in any sample or at any visit. As shown in Table 2, the mean endpoint $HAM\text{-}D_{17}$ score for the ITT sample was 10.8 (SD = 6.4) in the sertraline group and 9.7 (SD = 6.4) in the venlafaxine XR group ($F = 0.744$, $df = 1,142$; $p = NS$). Similar patterns were seen in the COMP and END-3 samples.

Groups in the ITT sample did not differ significantly in terms of rates of response (55% in sertraline, 65% in venlafaxine XR; $\chi^2 = 1.51$, $df = 1$, $p = .220$) or rates of remission (38% in sertraline, 49% in venlafaxine XR; $\chi^2 = 1.9$, $df = 1$, $p = .168$). Similarly, the COMP and END-3 samples showed no differences in rates of response or remission (Table 2).

Regression analyses with duration of illness, age, anxiety comorbidity, sex, and $HAM\text{-}D_{17}$ score as predictor variables were conducted separately for the baseline and week-8 Q-LES-Q scores in order to examine the relation between symptom severity and quality of life. At intake, the $HAM\text{-}D_{17}$ score and age were both significant predictors ($HAM\text{-}D_{17}$: $\beta = –0.227$, $t = –2.93$, $p < .01$; age: $\beta = 0.180$, $t = 2.35$, $p < .05$). Neither accounted for a significant amount of the variance in baseline Q-LES-Q score ($HAM\text{-}D_{17}$: $R^2 = 0.05$; age: $R^2 = 0.04$). However, at the end of the acute treatment phase, the amount of variance accounted for by the $HAM\text{-}D_{17}$ was much larger. In the ITT sample, the final $HAM\text{-}D_{17}$ score was the only significant predictor ($\beta = –0.661$, $t = –11.078$, $p < .001$) and accounted for 44% ($R^2 = 0.437$) of the variance in the final Q-LES-Q score. Similarly, results of a regression model using the change in Q-LES-Q from baseline to endpoint as the dependent variable and substituting the change in $HAM\text{-}D_{17}$ score from baseline to endpoint as a predictor variable indicated that the change in $HAM\text{-}D_{17}$ score was still the only significant predictor ($\beta = –0.578$, $t = –8.89$, $p < .001$) and accounted for 33% ($R^2 = 0.334$) of the variance.

Groups did not differ in final mean scores on either the CGI-S or the CGI-I in any sample, although trends favored venlafaxine XR for some comparisons. The final mean CGI-S score in the ITT sample for the sertraline group was 2.6 (SD = 1.1), compared with 2.4 (SD = 1.1)

Table 3. Most Common Adverse Events (≥ 10% occurrence) by Group

	Sertraline		Venlafaxine XR	
Event	Frequency[a]	%	Frequency[a]	%
None	15/74	20	16/75	21
Any autonomic[b]	33/72	46	39/71	55
Headache	16/72	22	23/71	32
Any gastrointestinal[c]	35/72	49	33/71	46
Nausea	12/72	17	12/71	17
Diarrhea	22/72	31	18/71	25
Any sleep disruption[d]	31/72	43	29/71	41
Insomnia	19/72	26	14/71	20
Any genitourinary[e]	20/72	28	20/71	28
Sexual side effects	15/72	21	16/71	23
Any musculoskeletal[f]	14/72	19	15/71	21

[a]The variability in sample numbers is due to missing data.
[b]"Any autonomic" includes headache, dizziness, dry mouth, and sweating. Headache was present in ≥ 10% of the sample.
[c]"Any gastrointestinal" includes nausea, vomiting, abdominal cramps, flatulence, altered taste, weight loss, appetite change, constipation, diarrhea, indigestion, and abdominal distress. Nausea and diarrhea were each present in ≥ 10% of the sample.
[d]"Any sleep disruption" includes insomnia, somnolence, hypersomnia, broken sleep, vivid dreams, and nightmares. Insomnia was the only individual symptom to be present in ≥ 10% of the sample.
[e]"Any genitourinary" includes increased frequency of urination, urine odor, difficulty urinating, low libido, ejaculatory delay, ejaculatory failure, delayed orgasm, and impotence. Together, the sexual symptoms were present in ≥ 10% of the sample.
[f]"Any musculoskeletal" includes muscle weakness, muscle cramps, twitch/fasciculations, tremors, myalgia, ataxia, akathisia, low back pain, and jaw discomfort. No individual symptom within this group was present in ≥ 10% of the sample.
Abbreviation: XR = extended release.

in the venlafaxine XR group (NS: $F = 0.976$, df = 1,143; $p = .325$). There was a trend for the venlafaxine XR group to have a higher CGI-I score at the final visit; the mean CGI-I score for the sertraline group was 2.3 (SD = 1.1), compared with 2.0 (SD = 1.1) for the venlafaxine XR group ($F = 2.75$, df = 1,144; $p = .10$). Forty-five percent of the sertraline group was rated as either "not ill" or "very mildly ill" on the final CGI-S, compared with 59% of the venlafaxine XR group (trend: $\chi^2 = 3.14$, df = 1, $p = .082$), and 61% of the sertraline group was rated as much or very much improved on the CGI-I, compared with 75% of the venlafaxine XR group (trend: $\chi^2 = 3.55$, df = 1, $p = .064$).

Groups did not differ significantly on final score or degree of improvement on the HAM-A in any sample. The final mean score in the sertraline group for the ITT sample was 9.1 (SD = 5.4), and for the venlafaxine XR group the mean score was 8.2 (SD = 5.7) ($F = 1.08$, df = 1,138; $p = .300$). Similar results were noted in the COMP and END-3 samples.

As shown in Table 3, the most common treatment-related adverse event categories for sertraline, in descending order, were gastrointestinal symptoms, autonomic symptoms, and sleep disruption; for venlafaxine XR, the most common symptom categories were autonomic symptoms, gastrointestinal symptoms, and sleep disruption. Groups did not differ on adverse events during acute treatment. Posttaper, more sertraline (25%) than venlafaxine XR (8%) patients reported diarrhea ($\chi^2 = 6.38$, df = 1, $p < .05$), and more venlafaxine XR patients (42%) than sertraline patients (23%) reported dizziness/faintness ($\chi^2 = 4.79$, df = 1, $p < .05$). Groups did not differ on emergence of other symptoms such as sleep, sensory, or autonomic problems after taper. Groups did not differ in the percentage of patients who tolerated taper such that they were off study medication within 2 weeks after the final visit (78% in each group).

DISCUSSION

The results of this double-blind study of people with major depressive disorder indicate that sertraline and venlafaxine XR produce comparable rates of improvement on both symptom and global quality-of-life measures. Final scores, remission rates, response rates, and rates of adverse events did not differ significantly between treatment groups. The putative dopaminergic effect of sertraline did not produce a superior effect relative to venlafaxine XR on the Q-LES-Q.

These findings, particularly with regard to nonsignificant differences in remission rates, are in contrast to the earlier meta-analytic comparisons of SSRIs to venlafaxine XR[9,11] and a previous head-to-head comparison of sertraline and venlafaxine XR.[23] On the other hand, the difference between groups in response and remission rates found in the current study is similar to that reported previously. In this study, the response and remission rates for the ITT sample were 65% and 49% for venlafaxine XR and 55% and 38% for sertraline, respectively, yielding a 10% difference in response rates and an 11% difference in remission rates. Mehtonen et al.[23] reported response rates for venlafaxine XR and sertraline of 83% and 68% and remission rates (defined as a HAM-D score less than 10) of 68% and 45%, respectively. Einarson et al.[11] reported response rates of 74% for venlafaxine XR and 61% for SSRIs. Thase et al.[9] showed remission rates of 45% and 35% for venlafaxine XR and SSRIs, respectively. It could be argued that since the absolute differences in rates of response and remission are similar to earlier studies, the lack of significant differences in the present study is related to low statistical power.

A goal of the study was to evaluate the relative effectiveness of optimal or maximal doses of the drugs, and group differences between the nonoptimized and optimal dosing samples are striking. Of patients who did not achieve maximum dose (225 mg/day for venlafaxine XR and 150 mg/day for sertraline) for 3 weeks or more, response and remission rates, respectively, were 56% and 47% for venlafaxine XR and 56% and 28% for sertraline. In patients who achieved and maintained optimal dosing for 3 weeks, response rates still showed about

10% difference (venlafaxine XR = 70%, sertraline = 59%). However, remission rates were similar (venlafaxine XR = 50%, sertraline = 48%). The Mehtonen et al.[23] study, which concluded that venlafaxine XR was significantly superior to sertraline in terms of both remission and response, used doses of 100 mg/day of sertraline (range 50–100 mg/day) and 150 mg of venlafaxine XR (range 75–150 mg/day); mean doses were not reported either in Mehtonen et al.[23] or in Thase et al.[9] Along a similar vein, Poirier and Boyer[33] reported the relative effectiveness of venlafaxine XR and paroxetine in patients who had failed to respond to 2 prior antidepressant trials. In their study, response and remission rates were 52% and 42% for venlafaxine XR versus 33% and 20% for paroxetine. However, the mean dose of venlafaxine XR was 269.0 mg/day and the mean dose of paroxetine was 36.3 mg/day. Together, these data raise the possibility that the differences in remission rates of this and other studies may have been due to discrepancies in mean doses. Therefore, future studies should take dose into consideration in terms of both design and analysis.

There are at least 2 reasons why a maximized trial of venlafaxine XR and sertraline produced equivalent remission rates. In addition to random variation in the data, as mentioned, it is possible that differences in prior analyses between venlafaxine XR and SSRIs were simply due to clinically meaningful differences in mean doses of drugs. Therefore, the differences in remission rates could have been the result of a lack of dosage comparability rather than overall effectiveness. It is also possible that, at higher doses, the noradrenergic effects of venlafaxine XR or putative dopaminergic effects of sertraline enhanced the therapeutic effect.

The patient population included in this study may also have had an effect on response. Both Mehtonen et al.[23] and the current study included patients of roughly equivalent initial severity (HAM-D score ≥ 18). However, whereas in Mehtonen et al. almost two thirds of the sample had been depressed for less than 7 months, less than half of the patients in the current study had been depressed that short a time. The impact of chronicity on treatment response is well known.[34] Thus, in a more chronic sample, overall response may be reduced, and any difference in effect between sertraline and venlafaxine XR may be lessened.

Previous work[24] has suggested that depression symptom measures may not account for much of the variance in the Q-LES-Q. If this is the case, quality of life and depressive symptoms might be expected to be independent constructs that demonstrate differential response to treatments. Of note, the recommendations of Rapaport et al.[24] were based on analysis of pretreatment measures only and did not measure any effects of treatment. In most depression studies, the range of Q-LES-Q scores prior to treatment is relatively limited. The limited range of quality-of-life scores might be expected to reduce the probability of detecting a correlation between pretreatment quality of life and depression measures. In this study, results similar to that of Rapaport et al.[24] were shown at baseline; the HAM-D_{17} score accounted for very little of the variance in Q-LES-Q ($R^2 = 0.05$). However, following treatment, when there was a higher range of variance in quality-of-life scores, the final HAM-D_{17} score accounted for 44% of the variance on the Q-LES-Q. Similarly, the baseline-to-endpoint change in HAM-D_{17} score accounted for 33% of the change in Q-LES-Q. Therefore, with endpoint and change values, the symptom measure accounted for a greater amount of the variance in Q-LES-Q score than the baseline measures. However, it should be emphasized that less than half of the Q-LES-Q variance was accounted for by the HAM-D_{17} measures, suggesting that the Q-LES-Q is at least partially independent of simple measurements of symptom severity and is consistent with the contention of Rapaport et al.[24]

In conclusion, this study suggests that, particularly at higher but clinically relevant doses, sertraline and venlafaxine XR are equally effective in the treatment of major depressive disorder and produce comparable improvements in response and remission rates as well as associated factors such as anxiety and quality of life. Future comparison trials will need to test the effects of dosing on rates of response and remission.

Drug names: desipramine (Norpramin and others), fluoxetine (Prozac and others), nortriptyline (Pamelor, Aventyl, and others), paroxetine (Paxil, Pexeva, and others), selegiline (Eldepryl and others), sertraline (Zoloft and others), venlafaxine (Effexor and others), zolpidem (Ambien).

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