# Venlafaxine Extended Release in the Short-Term Treatment of Depressed and Anxious Primary Care Patients With Multisomatoform Disorder

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***Objective:*** This pilot study explored the efficacy and tolerability of extended-release venlafaxine (venlafaxine ER) in anxious and/or depressed patients with multisomatoform disorder (MSD).

***Method:*** This 12-week, multicenter, randomized, double-blind study evaluated adult primary care outpatients with MSD and comorbid major depressive disorder, generalized anxiety disorder, or social anxiety disorder (DSM-IV criteria). The intent-to-treat population included 112 patients (venlafaxine ER, N = 55; placebo, N = 57). The primary efficacy variable was the change in the 15-item Patient Health Questionnaire (PHQ-15) somatic symptom severity score. Secondary outcomes included the Hamilton Rating Scale for Depression (HAM-D-17) and for Anxiety (HAM-A), Clinical Global Impressions-Severity of Illness (CGI-S) and -Improvement (CGI-I) scales, McGill Quality of Life Questionnaire Physical Symptoms Scale (MQOL-PS), and Medical Outcomes Study Short-Form 36-Item questionnaire (MOS SF-36). Data were collected from April 2003 to December 2003.

***Results:*** The decline by week 12 in PHQ-15 scores was significant ($p < .0001$) in both groups; however, the difference between the venlafaxine ER and placebo groups (–8.3 vs. –6.6, respectively) was not ($p = .097$). Improvement was greater with venlafaxine ER than placebo on the PHQ-15 pain subscale ($p = .03$), SF-36 bodily pain scale (26.1 vs. 14.5, $p = .03$), MQOL-PS (–11.7 vs. –6.0, $p = .02$), HAM-A psychic anxiety subscale ($p = .02$), SF-36 mental component summary ($p = .03$), time to response (54 vs. 71 days, $p = .01$), and CGI-I scale ($p = .009$). Venlafaxine ER was generally well tolerated.

***Conclusion:*** These results suggest that venlafaxine ER may be effective in relieving some types of somatic physical symptoms, particularly pain, in patients with depression and/or anxiety disorders.

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Approximately one third of somatic symptoms encountered in the primary care setting are medically unexplained.[1–5] Between 26% and 31% of primary care patients presenting with unexplained physical complaints have a comorbid depressive or anxiety disorder.[3,4,6–8] Somatic complaints are the predominant presentation for primary care patients with psychological distress,[9–11] with 70% to 90% of those with depression or anxiety complaining of somatic rather than psychological symptoms.[11] Multiple unexplained physical complaints increase the likelihood of psychiatric comorbidities,[10,12–14] and studies suggest that the number of unexplained physical symptoms, rather than the specific type of symptom, can indicate the presence of depressive or anxiety disorders.[3,4,12] Among patients with medically unexplained symptoms, as many as two thirds have a depressive disorder, and 40% to 50% have an anxiety disorder.[4]

Somatization disorder is present in 2% to 5% of primary care patients.[8,15,16] An abridged somatization dis-



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order diagnosis developed and validated by Escobar and colleagues[17,18] measures a less severe form of somatization and has a prevalence of 8% to 30% in primary care patients.[19] Despite the fact that somatization is associated with comorbid depressive or anxiety disorders, at least one third of patients have somatization alone.[8,14,18,20,21] Comparable to mood and anxiety disorders, somatoform disorders can adversely affect patient functioning and quality of life[16,22–24] and are responsible for increased costs as a result of greater health care utilization.[16,22–26] Primary care physicians may find that these patients are often difficult to treat.[22,26,27] Moreover, various domains of health-related quality of life are adversely affected, independent of comorbid depression and anxiety.[8,10,15]

The *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV), Primary Care Version,[28] has introduced a new diagnosis, multisomatoform disorder (MSD), which occupies a middle ground along the spectrum of somatization. Recognized as a "moderately severe form of undifferentiated somatoform disorder,"[29] MSD requires the presence of at least 3 out of 15 symptoms that are currently bothersome (i.e., in the past 2 weeks), along with a 2-year history of somatization.[22] With a prevalence rate of 8% to 10% among primary care patients, MSD is much more common than somatization disorder but is associated with comparable levels of impairment.[22,30] Patients with MSD are at increased risk for a comorbid depressive and/or anxiety disorder[3,31] and are more likely to report unmet expectations after the visit, to be perceived by their providers as difficult, and to have persistent psychiatric symptoms and ongoing stress months after their initial visit.[3,4,12,22,32,33] Indeed, MSD has a substantial and independent effect on functioning and health care utilization, even after controlling for depressive and anxiety disorders.[22] Because it depends principally on current symptoms (i.e., the 2-year history of somatization can generally be deduced from medical records or a global question by the clinician), the diagnosis of MSD may have greater clinical utility and reliability than a diagnosis of a disorder that is based on lifetime recall of numerous individual symptoms[34,35] (e.g., full or abridged somatization disorder). It is worth noting that most patients (88% to 95%) with MSD also meet criteria for full or abridged somatization disorder.[25,30]

There are limited data on the efficacy of antidepressants or other pharmacotherapy for the spectrum of somatoform disorders. Evidence has emerged suggesting that the extended-release (ER) serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine (venlafaxine ER) may not only be more effective than selective serotonin reuptake inhibitors (SSRIs) in treating symptoms of depression[36,37] but may also have some benefits in treating pain and other somatic symptoms, while showing similar safety and tolerability.[38–40] Randomized, controlled trials have demonstrated the efficacy of venlafaxine ER in the treatment of major depressive disorder (MDD),[36,37] generalized anxiety disorder (GAD),[41–44] social anxiety disorder (SAD),[45] panic disorder,[46] posttraumatic stress disorder,[47] mixed depression and anxiety states,[48,49] and neuropathic pain.[39,40] Recently, the use of venlafaxine for treating pain associated with neuropathy, MDD or GAD, headache, fibromyalgia, and postmastectomy pain syndrome has been examined.[38] The purpose of this pilot study is to examine the efficacy and safety of venlafaxine ER compared with placebo in treating physical and emotional symptoms in depressed and/or anxious patients with MSD.

## METHOD

### Participants

Study participants were outpatients 18 years or older who:

- Met DSM-IV diagnostic criteria for MDD, GAD, and/or SAD, as measured by the Mini-International Neuropsychiatric Interview (MINI).[50]
- Met clinical criteria for MSD, as measured by the 15-item Patient Health Questionnaire (PHQ-15) (i.e., had 3 or more medically unexplained symptoms with a frequency or severity beyond that expected for a known medical condition, with more than 1 of these symptoms present for at least 6 months).[22]
- Had a 17-Item Hamilton Rating Scale for Depression (HAM-D-17)[51] total score of at least 14 and a Hamilton Rating Scale for Anxiety (HAM-A)[52] total score of at least 12 at screening.
- Had no more than a 25% decrease in total HAM-D-17 score or total HAM-A score from screening to randomization. The rationale for this requirement was to confirm that the patient's depression or anxiety was stable so that change in symptoms of MSD could be attributed to treatment rather than fluctuations in the course of the comorbid disorder.

Exclusion criteria included a history of inability to tolerate or failure to respond to 2 or more antidepressants of sufficient dose and duration of administration for the treatment of symptoms present in the current illness (depressive or anxiety); a current or past history of mania, bipolar disorder, schizophrenia, or other psychotic disorder; a history of seizure disorder other than childhood febrile seizure; evidence of a serious or clinically unstable medical illness or psychiatric condition that could compromise participation in the study; previous intolerance or hypersensitivity to venlafaxine or venlafaxine ER; use of any nonpsychopharmacologic drug with psychotropic effects within 7 days of study randomization, a monoamine oxidase inhibitor or fluoxetine within 30 days of screening, or

electroconvulsive therapy within 3 months of screening; chronic use of analgesics containing opiates for > 6 months or for ≥ 3 consecutive weeks prior to screening; known or suspected alcohol or drug abuse within 6 months of screening; use of triptans, psychoactive herbal medications, or any other psychoactive drugs; or a positive urine drug test (e.g., amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, methadone, methaqualone, opiates, and propoxyphene) at screening. Women who were breast feeding or pregnant, who expected to become pregnant during the course of the study, or who were sexually active and were not using birth control were also excluded.

Permitted concomitant pharmacologic treatments were zaleplon, zolpidem, or zopiclone (1 dose nightly) as needed for insomnia for up to 6 nights during the 14 days immediately following randomization and short-term treatments for symptoms of allergies, colds, or influenza, provided the medications utilized had no psychotropic effects. Patients were not excluded if they had ever taken venlafaxine ER, and data are not available comparing the number of patients in each group who had prior exposure to venlafaxine. The proportion of patients in each group who took at least 1 concomitant medication was almost identical (venlafaxine ER, 63.6%, vs. placebo, 63.3%). Likewise, the numbers of patients taking analgesics were similar between the venlafaxine ER and placebo groups, including nonsteroidal anti-inflammatory drugs (10 vs. 13), acetaminophen (7 vs. 9), COX-2 inhibitors (8 vs. 3), and salicylates (4 vs. 4).

### Study Design

This was a randomized, double-blind, placebo-controlled study, with outpatients recruited from 19 sites throughout the United States that provide primary care or general medical services. Data were collected from April 2003 to December 2003. Patients underwent a 1- to 2-week screening phase, followed by randomization to treatment with flexible-dose venlafaxine ER or placebo for 12 weeks, with up to 2 weeks of taper. Participants were scheduled for 8 clinic visits: screening; baseline; weeks 1, 2, 4, 8, and 12; and posttaper. Patients who discontinued treatment prematurely completed all week 12 procedures within 4 days after their last dose of study drug.

Dosing during the 12-week treatment phase was as follows: week 1, 75 mg venlafaxine ER or matching placebo q.d. (1 capsule); week 2, 150 mg venlafaxine ER or matching placebo q.d. (2 capsules taken in 1 dose); weeks 3 through 12, 225 mg venlafaxine ER or matching placebo q.d. (3 capsules taken in 1 dose), up to a maximum of 225 mg. Dose titration was based on drug tolerability and patient response. Patients who could not tolerate a particular dose were decreased by 1 capsule q.d. until a tolerable dose had been reached. Once the dose had been decreased due to poor tolerability, it was not increased again during the trial. Patients who could not tolerate at least 75 mg q.d. (1 capsule), at any time during the study, were withdrawn from the study. Patients could voluntarily withdraw from the study at any time; those who withdrew were not replaced, regardless of reason for withdrawal, but were asked to complete week 12 procedures. The study, including the provision of written informed consent by all participants, was conducted in accordance with the Declaration of Helsinki and its amendments.

In this study, a symptom was defined as medically "unexplained" if, in the opinion of the evaluating physician, it was (1) idiopathic, and after standard medical evaluation, the causation remained unknown, or (2) a symptom characteristic of a known medical disorder but reported at a frequency or severity considered out of proportion to that expected for the known medical condition.

### Efficacy Measures

The primary efficacy measure was the PHQ-15 somatic symptom severity score,[53] which was measured at screening, baseline, and weeks 4, 8, and 12. The PHQ-15 was chosen because it (1) comprises the somatic symptoms that account for more than 90% of all nonrespiratory physical complaints in primary care; (2) has been validated in 6000 patients from 8 primary care and 7 obstetric-gynecology outpatient settings; (3) is strongly associated with multiple domains of functional status, health-related quality of life, and health care use; (4) corresponds to the symptom criterion required to establish a diagnosis of MSD; and (5) has preliminary evidence suggesting it is responsive to change in depressed patients undergoing antidepressant treatment.[54]

The subset of items comprising the PHQ-15 measures the following somatic symptoms: stomach pain; back pain; pain in the arms, legs, or joints (knees, hips, etc.); menstrual cramps or other problems with periods (women only); headaches; chest pain; dizziness, fainting spells; feeling one's heart pound or race; shortness of breath; pain or problems during sexual intercourse; constipation, loose bowels, or diarrhea; nausea, gas, or indigestion; feeling tired or having low energy; and trouble sleeping. The total score ranges from 0 to 30, with higher numbers representing greater somatic symptom severity. Instructions to the patient ask, "During the past 4 weeks, how much have you been bothered by any of the following problems?" Scale items are scored from 0 to 2, with 0 corresponding to "not bothered at all," 1 corresponding to "bothered a little," and 2 corresponding to "bothered a lot." Improvement in PHQ-15 score in this study was assessed both as a continuous variable (mean change from baseline to end of study) as well as a categorical outcome (i.e., a response, defined as a final PHQ-15 score lower than 10).

Secondarily, we examined response to the PHQ-15 pain and nonpain subscales, both of which have proven responsive to change in depressed patients undergoing antidepressant treatment.[54] Also, the PHQ-15 pain and the Medical Outcomes Study Short-Form 36-Item questionnaire (MOS SF-36) bodily pain scales have similar predictive validity.[55] Other secondary efficacy measures included the HAM-D-17,[51] HAM-A,[52] Clinical Global Impressions-Severity of Illness scale (CGI-S) and Clinical Global Impressions-Improvement scale (CGI-I),[56] McGill Quality of Life Questionnaire Physical Symptoms Scale (MQOL-PS),[57] MOS SF-36,[58] and Medical Outcomes Study Concentration Scale (MOS-CS).[59] The HAM-D-17 and HAM-A were measured at screening, baseline, and weeks 2, 4, 8, and 12; the CGI-S was measured at baseline and weeks 2, 4, 8, and 12 (the CGI-I was measured during the same visits but not at baseline); and the MQOL-PS, MOS SF-36, and MOS-CS were measured at baseline and week 12.

### Safety Assessments

A complete physical examination was performed: weight was recorded and blood chemistry, hematology, urinalysis, thyroid-stimulating hormone testing, urine drug screen, and electrocardiography were performed at screening and week 12. Height was measured at screening, and a pregnancy test was administered to women of childbearing age at screening, baseline, and week 12. Supine vital signs (heart rate and blood pressure), adverse events (from the time that the informed consent was signed to 30 days following the last dose of study medication), and prior and concomitant treatments were recorded at all visits, including the visit after the taper following the double-blind treatment phase, during which efficacy outcomes were assessed.

### Statistical Methods

All efficacy analyses were performed in the intent-to-treat (ITT) population, which included patients who had at least 1 postbaseline efficacy evaluation. The primary efficacy endpoint was the change in PHQ-15 total score from baseline to week 12 or the final visit. For patients who discontinued the study, change from baseline was based on the final recorded score (last-observation-carried-forward [LOCF] analysis). In addition to LOCF analysis, observed changes at each visit were examined. The primary efficacy endpoint was evaluated using an analysis of covariance (ANCOVA) model with treatment group as the main effect and baseline value as the covariate. No adjustment for study site was made.

A preliminary model was performed that included a term for baseline-by-treatment interaction to test the assumption of parallel slopes, which would indicate the absence of an interaction effect. If a significant baseline-by-treatment interaction was found using this preliminary model (alpha = 0.10), an analysis of variance (ANOVA) model with effect of treatment was used to analyze the treatment difference on total score with no adjustment for baseline. p Values and the 95% confidence interval (CI) for the treatment difference based on the ANCOVA/ANOVA model were then reported.

As an exploratory analysis, a mixed model with treatment, time, and treatment-by-time interaction as fixed effects and patient as random effect was used to analyze the PHQ-15 total scores. For the mixed model, a covariance structure for unequally spaced data was adopted to account for the possible correlation between multiple observations from the same patient. The continuous secondary efficacy variables (HAM-D-17, HAM-A, MQOL-PS, MOS SF-36, MOS-CS, and CGI-S) were analyzed using the same ANCOVA/ANOVA approach described for the primary efficacy variable (the CGI-I was analyzed using ANOVA, since patients had no baseline score on this variable). Categorical variables, such as response rate, were analyzed using the Fisher exact test. The odds ratio and an exact 95% CI were also computed. Time to response was analyzed using the Kaplan-Meier method. For systolic and diastolic blood pressure, within-group differences were analyzed using paired t tests, and between-group differences were compared using the ANCOVA model. No adjustment was made for multiple comparisons. Thus, between-group differences in outcomes should be interpreted with caution.

There was no previous information on the magnitude of the effect of venlafaxine on the primary endpoint in this patient population or the variability of the response. Thus, the sample size was based on estimate of effect size that would be considered clinically significant. It was estimated that 50 subjects per group would provide approximately 90% power to detect an effect size of 0.66 (alpha = 0.05, 2-sided).

## RESULTS

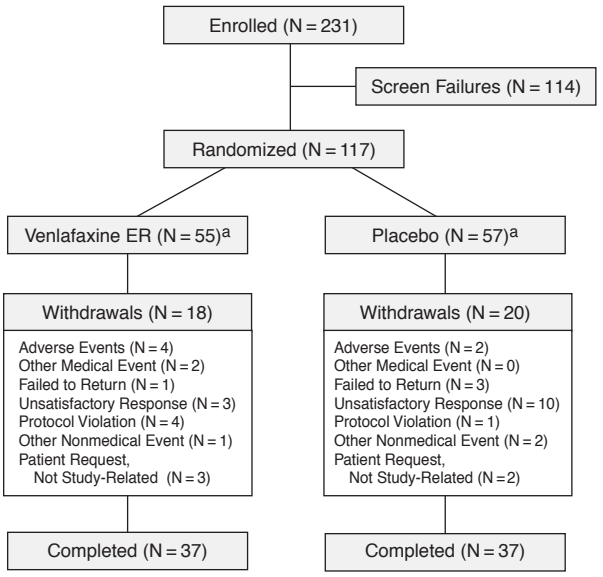
### Patient Characteristics

One hundred seventeen patients met the eligibility requirements and were randomly assigned to treatment with flexible-dose venlafaxine ER or placebo; 112 patients (venlafaxine ER, N = 55; placebo, N = 57) were included in the ITT population, as shown in Figure 1. Baseline characteristics were similar between groups (Table 1).

### Efficacy

Figure 2 shows the changes in total PHQ-15 scores over the course of the study. At week 12, the venlafaxine ER and placebo groups both showed a significant reduction ($p < .0001$) in PHQ-15 scores (–8.3 and –6.6, respectively) from baseline, indicating improvement, but the difference between groups was not significant ($p = .097$). The response rate (i.e., achieving a PHQ-15 total score < 10)

Figure 1. Study Flow Chart




[a]Intent-to-treat population.
Abbreviation: ER = extended release.

Table 1. Baseline Demographic Characteristics and Scale Scores of 112 Anxious and/or Depressed Patients With Multisomatoform Disorder[a]

| Characteristic | Venlafaxine ER (N = 55) | Placebo (N = 57) |
|---|---|---|
| Demographic | | |
| Gender, N (%) | | |
| Male | 7 (13) | 15 (26) |
| Female | 48 (87) | 42 (74) |
| Race/ethnicity, N (%) | | |
| Asian | 0 (0.0) | 1 (1.8) |
| Black | 8 (14.5) | 3 (5.3) |
| Native Hawaiian/ Pacific Islander | 1 (1.8) | 0 (0.0) |
| White | 42 (76.4) | 47 (82.5) |
| Hispanic/Latino | 4 (7.3) | 6 (10.5) |
| Age, mean (SD), y | 47 (11) | 47 (13) |
| Scale score, mean (SD) | | |
| PHQ-15 total | 18.0 (3.4) | 18.1 (3.2) |
| PHQ-15 pain | 6.5 (1.77) | 6.6 (1.57) |
| PHQ-15 nonpain | 11.5 (2.2) | 11.5 (2.8) |
| HAM-D-17 total | 24.8 (4.7) | 23.9 (5.8) |
| HAM-A total | 29.0 (7.9) | 29.3 (8.8) |
| CGI-S | 4.6 (0.7) | 4.6 (0.7) |
| MQOL-PS total | 29.9 (5.4) | 28.6 (5.8) |
| MOS SF-36 physical health | 42.0 (16.2) | 43.4 (17.2) |
| MOS SF-36 mental health | 26.6 (13.7) | 28.3 (14.5) |
| MOS-CS | 39.2 (20.2) | 39.5 (22.8) |

[a]All patients in both groups met the baseline anxiety cutoff (HAM-A score ≥ 12) for study entry, and 55 of 57 patients in the placebo group met the baseline depression cutoff (HAM-D-17 score ≥ 14). There were no significant differences between groups in comorbidity measured by either scale.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, ER = extended release, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D-17 = 17-Item Hamilton Rating Scale for Depression, MOS-CS = Medical Outcomes Study Concentration Scale, MOS SF-36 = Medical Outcomes Study Short-Form 36-Item Questionnaire, MQOL-PS = McGill Quality of Life Questionnaire Physical Symptoms Scale, PHQ-15 = 15-Item Patient Health Questionnaire.

was greater in the venlafaxine ER group and approached statistical significance (51% vs. 37%, p = .08), and the median time to response was faster (54 vs. 71 days, p = .01).

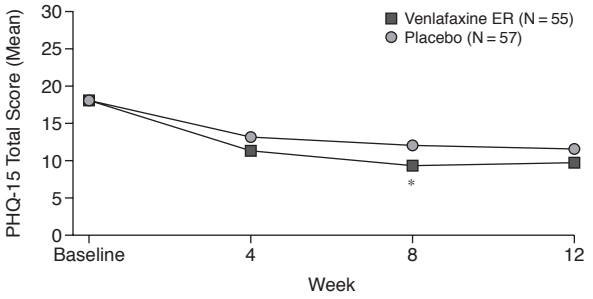
Venlafaxine ER showed greater improvement than placebo on the PHQ-15 pain subscale (p = .03) but not on the PHQ-15 nonpain subscale (Table 2). The venlafaxine ER group also showed greater improvement on the MOS SF-36 bodily pain scale (26.1 vs. 14.5, p = .03) and the MQOL-PS scale (–11.7 vs. –6.0, p = .01). Other secondary outcomes for which venlafaxine ER proved superior included the HAM-A psychic anxiety, MOS SF-36 mental component summary, MOS-CS, and CGI-I scores. Outcomes for the other measures showed significant (p < .01 or better) improvement in both the venlafaxine ER and placebo groups (Table 2), with all between-group differences favoring venlafaxine ER but not achieving significance.

There are several points worth noting from Table 3, which shows the percentages of patients who reported that they were bothered by individual somatic symptoms assessed by the PHQ-15 at baseline and after 12 weeks of treatment with venlafaxine ER or placebo. First, the percentages of patients who reported that they were bothered for most of these symptoms at baseline were high and were similar in both groups. Second, the percentages declined substantially for most symptoms by week 12. Third, the decline in the percentage of patients who reported being bothered was greater with venlafaxine ER for most symptoms, achieving significance for stomach pain (p = .03) and headache (p = .03).

## Safety

There was no significant difference between the venlafaxine ER group (N = 18) and placebo group (N = 20) in the number of patients who withdrew from the study, and the duration of study participation was similar between the 2 groups. The average prescribed dose for venlafaxine ER was 177 mg/day and the maximum prescribed daily dose was 209 mg/day, with the latter ranging from 75 mg/day to 225 mg/day. As shown in Table 4, venlafaxine ER showed a somewhat higher incidence than placebo of treatment-emergent adverse effects, with more than 10% of venlafaxine ER patients experiencing nausea, headache, fatigue, dizziness, constipation, and tremor. At the final visit, patients in the venlafaxine ER group showed a clinically nonsignificant mean decrease in weight, and patients in the placebo group showed a clinically nonsignificant increase, although the difference between groups was significant (p = .03). Baseline-to-endpoint changes in cholesterol levels were almost identical for the 2 groups. As shown in Table 5, cardiovascular effects were also similar in both groups. There were no clinically signifi-

**Figure 2. 15-Item Patient Health Questionnaire (PHQ-15) Total Score, Last Observation Carried Forward**




*p < .01 vs. placebo.
Abbreviation: ER = extended release.

cant within-group or between-group baseline-to-endpoint changes in pulse, systolic blood pressure, or diastolic blood pressure. Also, pulse rate, QRS, and QTc intervals were similar between the 2 groups.

## DISCUSSION

The primary efficacy endpoint in this study—the mean PHQ-15 total score change following treatment—did not show a statistically significant difference between the venlafaxine ER and placebo treatment groups. The response rate (i.e., PHQ-15 total score < 10) tended to be greater in venlafaxine ER–treated patients (51% vs. 37%, p = .08), and their median time to response was also shorter (54 vs. 71 days, p = .01). Indeed, improvement was greater in the venlafaxine ER group than in the placebo group on all measures (Table 2), although the difference between groups was not statistically significant in all cases. This may be due, in part, to the small sample size of this pilot study, the modest magnitude of some between-group differences, the diverse diagnoses of study participants (MDD, GAD, SAD), or the heterogeneous somatic symptoms of MSD patients.

The strongest evidence for the PHQ-15 is for its use as a screening tool for somatic symptoms and as a measure of symptom severity.[53] While there are preliminary data from 1 study suggesting the potential responsiveness of the PHQ-15 to antidepressant treatment,[54] this has not yet been well established. Thus, it is possible that the PHQ-15 lacks sufficient sensitivity to detect changes in somatic symptom severity following treatment, especially in view of the fact that several other outcome measures did show differences between the venlafaxine ER and placebo groups. In addition, while the withdrawal rates between the venlafaxine ER and placebo groups were similar, the somewhat higher incidence of treatment-emergent adverse effects, including nausea, headache, fatigue, dizziness, constipation, and tremor, in the active treatment group may have

**Table 2. Baseline-to-Endpoint Changes in Outcome Measures (ITT population)**

| Measure | Venlafaxine ER (N = 55) | Placebo (N = 57) | p Value[a] |
|---|---|---|---|
| Response rate (LOCF), N (%)[b] | 28 (50.9) | 21 (36.8) | .08 |
| Time to response, median, d[c] | 54.0 | 71.0 | .01 |
| Scale, mean change (SD) | | | |
| PHQ-15 pain[d] | –3.3 (2.35) | –2.6 (2.15) | .03 |
| PHQ-15 nonpain[d] | –5.5 (2.87) | –4.6 (4.82) | .50 |
| HAM-D-17 total[d] | –13.2 (8.4)* | –9.6 (10.2)* | .07 |
| HAM-D-17 somatic subscale[d] | –2.4 (1.8)* | –1.9 (2.3)* | .34 |
| HAM-A total (final visit)[d] | –15.2 (9.7)* | –11.8 (11.1)* | .07 |
| HAM-A psychic anxiety[d] | –8.6 (5.6)* | –5.9 (6.1)* | .02 |
| HAM-A somatic anxiety[d] | –6.7 (5.2)* | –5.9 (5.7)* | .34 |
| CGI-S score (final visit)[d] | –1.8 (1.4)* | –1.4 (1.4)* | .15 |
| CGI-I score (final visit)[d] | –1.8 (1.4)* | –1.4 (1.4)* | .009 |
| MQOL-PS total[d] | –11.7 (10.5)* | –6.0 (10.9)** | .01 |
| MOS SF-36 physical health[e] | +19.5 (18.4)* | +12.7 (20.4)* | .09 |
| MOS SF-36 mental health[e] | +28.6 (24.1)* | +16.8 (25.2)* | .03 |
| MOS SF-36 bodily pain[e] | +26.1 (26.6)* | +14.5 (23.6)* | .03 |
| MOS-CS[e] | +30.1 (27.6)* | +15.3 (29.7)** | .007 |

[a]Baseline-to-endpoint change between groups.
[b]Response is defined as a PHQ-15 total score less than 10.
[c]The median is the Kaplan-Meier estimate.
[d]Lower scores are better.
[e]Higher scores are better.
*p < .0001, baseline-to-endpoint change within groups.
**p ≤ .001, baseline-to-endpoint change within groups.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, ER = extended release, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D-17 = 17-Item Hamilton Rating Scale for Depression, ITT = intent-to-treat, LOCF = last observation carried forward, MOS-CS = Medical Outcomes Study Concentration Scale, MOS SF-36 = Medical Outcomes Study Short-Form 36-Item Questionnaire, MQOL-PS = McGill Quality of Life Questionnaire Physical Symptoms Scale, PHQ-15 = 15-Item Patient Health Questionnaire.

confounded the comparison with placebo, since patients with MSD may amplify somatic cues.

There have been far fewer studies examining the efficacy of pharmacotherapy for somatoform disorders than studies examining the efficacy of pharmacologic treatment for depressive, anxiety, and other mental disorders. Two published trials, each a 6-week, randomized, placebo-controlled study, evaluated the efficacy of St. John's wort in patients with somatization disorder (ICD-10), undifferentiated somatoform disorder, or somatoform autonomic dysfunction without depression.[60,61] Each study showed that St. John's wort was more effective than placebo in reducing somatoform symptoms. One pilot study in 35 patients with somatoform pain disorder found a moderate analgesic benefit of citalopram compared with reboxetine.[62]

Pain-related symptoms are of particular interest, given that more than half of depressed patients experience pain and more than one fourth of pain patients report depression.[63] Additionally, pain is a risk factor for poor treatment response in depression,[63] and pain and anxiety frequently occur together and have reciprocal adverse effects on one another.[63,64] Evidence suggests that tricyclic antidepressants (TCAs) such as imipramine and amitripty-

**Table 3. Percentage of Patients Rating Individual PHQ-15 Symptoms as Bothersome[a] at Baseline and at Week 12**

| | Baseline | | 12 Weeks | |
|---|---|---|---|---|
| Symptom | Venlafaxine ER (N = 55), % | Placebo (N = 57), % | Venlafaxine ER (N = 55), % | Placebo (N = 57), % |
| Fatigue | 100 | 100 | 78 | 75 |
| Sleep complaints | 98 | 97 | 67 | 67 |
| Back pain | 95 | 88 | 60 | 74 |
| Arm or leg pain | 91 | 92 | 62 | 70 |
| Nausea, gas, or indigestion | 91 | 98 | 60 | 70 |
| Headache | 89 | 93 | 47* | 72 |
| Palpitations | 87 | 84 | 42 | 53 |
| Constipation or diarrhea | 87 | 91 | 67 | 68 |
| Stomach pain | 86 | 93 | 47* | 72 |
| Dyspnea | 76 | 70 | 36 | 51 |
| Dizziness | 71 | 68 | 38 | 40 |
| Chest pain | 60 | 68 | 22 | 26 |
| Menstrual pain or problems[b] | 46 | 40 | 29 | 36 |
| Sexual pain or problems | 44 | 54 | 27 | 23 |
| Fainting | 13 | 7 | 4 | 11 |

[a]Rating of "bothersome" = PHQ-15 item score of 1 ("bothered a little") or 2 ("bothered a lot").
[b]Denominator includes women only, receiving venlafaxine ER (N = 48) or placebo (N = 42).
*$p < .05$.
Abbreviations: ER = extended release, PHQ-15 = 15-item Patient Health Questionnaire.

**Table 4. Commonly Reported Treatment-Emergent Adverse Events[a]**

| Adverse Event | Venlafaxine ER (N = 55), N (%) | Placebo (N = 57), N (%) |
|---|---|---|
| Nausea | 16 (29.1) | 9 (15.8) |
| Headache | 13 (23.6) | 7 (12.3) |
| Fatigue | 8 (14.5) | 1 (1.8) |
| Dizziness | 6 (10.9) | 3 (5.3) |
| Constipation | 6 (10.9) | 3 (5.3) |
| Tremor | 6 (10.9) | 0 (0.0) |
| Back pain | 5 (9.1) | 1 (1.8) |
| Contusion | 4 (7.3) | 0 (0.0) |
| Decreased appetite | 3 (5.5) | 1 (1.8) |
| Hypoesthesia | 3 (5.5) | 0 (0.0) |
| Upper abdominal pain | 3 (5.5) | 0 (0.0) |
| Yawning | 3 (5.5) | 0 (0.0) |
| Nasopharyngitis | 2 (3.6) | 1 (1.8) |
| Migraine | 2 (3.6) | 1 (1.8) |
| Urinary tract infection | 2 (3.6) | 1 (1.8) |

[a]Occurring with a frequency of 10% in any treatment group, or with a frequency observed in the venlafaxine extended release (ER) group at least 2 times the frequency observed in the placebo group.

**Table 5. Changes in Blood Pressure and QTc Interval From Baseline to Week 12, Final Visit**

| Characteristic | Venlafaxine ER (N = 55) | Placebo (N = 57) |
|---|---|---|
| Systolic blood pressure, mm Hg | | |
| Mean | –1.7 | –0.7 |
| Median | –3 | –3 |
| Diastolic blood pressure, mm Hg | | |
| Mean | +1.7 | –1.7 |
| Median | +2 | –1 |
| QTc interval, ms | | |
| Mean | –0.9 | –1.5 |
| Median | –1.5 | –3 |

Abbreviation: ER = extended release.

line, which affect both serotonergic and noradrenergic pathways, are effective in ameliorating chronic pain, while SSRIs, which are safer and more tolerable than TCAs, are minimally effective.[65–67]

Like some TCAs, the SNRI venlafaxine ER has both serotonergic and noradrenergic effects that could be similarly beneficial for the treatment of painful symptoms. The fact that our pilot study found some indication of pain reduction following the initiation of venlafaxine ER treatment is consistent with evidence linking the common neurologic pathways and efficacy of drugs that modulate both noradrenergic and serotonergic activity in the treatment of pain and depression,[63,64,68–70] along with specific evidence for the efficacy of venlafaxine ER in the treatment of neuropathic and other types of pain.[38–40,71] The average prescribed venlafaxine ER dose of 177 mg/day and the maximum prescribed dose range of 75 mg/day to 225 mg/day used in our study were within the dose range recommended for venlafaxine ER's U.S. Food and Drug Administration (FDA)-approved indications for MDD, GAD, and SAD.

With regard to the statistically significant differences found between the active treatment and placebo groups observed in this study, several limitations should be acknowledged. First, the between-group difference in our primary outcome (PHQ-15 total score) was not statistically significant, and the significant differences found on various secondary outcomes (including pain) should be interpreted cautiously until confirmed in subsequent studies. Second, we studied somatizing patients with concurrent depression or anxiety. Therefore, one must be cautious in extrapolating our results to somatization in the absence of depression or anxiety, although previous meta-analyses have suggested that antidepressants may have a salutary effect on somatic symptoms independent of their effect on psychological symptoms.[66,72] Third, the heterogeneous symptom patterns seen in somatoform disorders may mean that both the type of disorder as well as individual symptoms (e.g., pain vs. nonpain) may have differential response to specific types of pharmacotherapy.

## CONCLUSION

The results of this study suggest that venlafaxine ER was generally well tolerated and showed significantly greater improvement than placebo on some measures of global clinical improvement, patient-rated pain symptoms, and functional status in the mental health domain. This is one of the few randomized, placebo-controlled

drug efficacy trials conducted on a group of patients sharing a single validated diagnosis of a somatization spectrum disorder—in this case, multisomatoform disorder. With the exception of the small trial comparing 2 antidepressants for somatoform pain disorder,[66] our study also appears to be the first randomized, placebo-controlled trial of a pharmacologic agent for the treatment of a disorder within the somatization spectrum with an FDA-approved indication for any psychiatric disorder. Overall, our pilot study suggests that venlafaxine ER may be effective in relieving some types of somatic physical symptoms, particularly pain, in patients with depression and/or anxiety disorders. Further trials with larger numbers of patients are warranted to better determine the efficacy of venlafaxine and other antidepressants for treatment of somatization in patients with MSD, or other populations and subgroups, based on diagnostic criteria for somatization, psychiatric comorbidities such as anxiety and depression, and other important screening criteria. Such studies would also be helpful in assessing the usefulness of diagnostic measures of somatization, such as MSD, in the evaluation of drug treatment efficacy.

*Drug names:* citalopram (Celexa and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), propoxyphene (Darvon and others), venlafaxine (Effexor), zaleplon (Sonata), zolpidem (Ambien), zopiclone (Lunesta).

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