A Pooled Analysis of Gender and Trauma-Type Effects on Responsiveness to Treatment of PTSD With Venlafaxine Extended Release or Placebo

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Objective: To examine effects of gender and trauma type on response to treatment with venlafaxine extended release (ER) or placebo in patients with posttraumatic stress disorder (PTSD).

Method: Data were pooled from 2 flexible-dose, parallel-group, randomized, double-blind, placebo-controlled trials: a 12-week trial conducted in the United States (March 2001 to December 2002) and a 24-week trial conducted in 12 countries outside the United States (October 2001 to December 2003). Six hundred eighty-seven outpatients with DSM-IV–diagnosed PTSD and a 17-item Clinician-Administered PTSD Scale abbreviated 1-week Symptom Status version (CAPS-SX-17) score ≥ 60 were randomly assigned to treatment with venlafaxine ER (37.5 mg/day–300 mg/day, N = 340) or placebo (N = 347). The primary efficacy end point was the CAPS-SX-17 total score at week 12. Secondary end points included CAPS-SX-17 cluster scores for reexperiencing, avoidance/numbing, and hyperarousal and scores on the Connor-Davidson Resilience Scale (CD-RISC), Clinical Global Impressions-Severity of Illness scale, Sheehan Disability Scale (SDS), and 17-item Hamilton Rating Scale for Depression (HAM-D-17). Analysis-of-covariance models were used to test for differences by gender and trauma type (accidental injury, combat, nonsexual abuse, adult sexual abuse, childhood sexual abuse, unexpected death, and other), treatment (venlafaxine ER vs. placebo), and the treatment-by-trauma-type interaction.

Results: Using last-observation-carried-forward analysis, significant effects of treatment with venlafaxine ER were found on the CAPS-SX-17 total score and on all CAPS-SX-17 cluster scores and most other secondary measures. No significant treatment-by-gender interactions were observed. Trauma type significantly affected treatment responsiveness on symptom-related disability (SDS, p = .0057) and resilience (CD-RISC, p = .0012), with a nearly significant effect on depression (HAM-D-17, p = .0625).

Conclusion: Overall, there does not appear to be a significant effect of gender on the efficacy of venlafaxine ER in the treatment of PTSD. Trauma type may affect treatment outcome but seems to affect domains such as disability and resilience more than core PTSD symptoms.

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Posttraumatic stress disorder (PTSD) imposes a substantial burden on the individual and society[1] through its association with psychiatric[2] and medical[3] comorbidities, suicidality and suicidal behavior,[4–6] lost productivity,[1] mental health service utilization,[7] and poor physical health.[8] The lifetime prevalence of DSM-III-R PTSD has been estimated to be 7.8%[2] based on the National Comorbidity Survey, a random sampling of the general population of the United States. Roughly twice as many women (10.4%) as men (5.0%) reported having had the disorder, despite the fact that more men (60.7%) than women (51.2%) reported having been exposed to a

traumatic event, and roughly twice as many men as women reported having experienced 3 or more exposures to traumatic events.[2] The 1996 Detroit Area Survey of Trauma[9] found similar results using DSM-IV criteria for PTSD. Both studies found that women were more likely than men to experience PTSD across most trauma types, although the risk of PTSD differed by trauma type and gender.

Other evidence also suggests that the symptom burden, course of illness, and impairment in quality of life associated with PTSD are all greater in women than in men.[10] Women experience substantially higher rates of rape and intimate partner violence than men, however, so it is unclear whether the higher prevalence of PTSD and greater severity (found in some studies) is attributable to greater exposure to certain more insidious types of trauma[11] or to gender-specific vulnerability factors.[12] Such vulnerability factors may include early adverse life experiences,[13] hormonal factors, or perceptual-cognitive processing of and/or behavioral responses to trauma-related information.[10] The gender difference in the prevalence of PTSD may also be partly explained by women being more likely to report PTSD symptoms and to seek treatment than men.[14]

Trauma type and gender may affect responsiveness to pharmacotherapy for PTSD and thus carry important implications for treatment, but few studies have examined the effects of these factors on treatment outcomes. Selective serotonin reuptake inhibitors (SSRIs) are generally considered an effective first-line pharmacologic treatment for PTSD.[15–18] However, treatment outcomes in clinical trials of SSRIs have not been entirely satisfactory or consistent across trauma types, and there remains a need for other treatments with a wider spectrum of efficacy across various types of PTSD patients. For example, there is evidence to suggest that combat-related PTSD may be less responsive to SSRI treatment than non–combat-related PTSD.[19–21] In addition, evidence of gender- and age-based differences in response to SSRIs in treatment of major depressive disorder (MDD)[22,23] raises the possibility of similar effects in the treatment of anxiety disorders.

Venlafaxine extended release (ER) is a serotonin-norepinephrine reuptake inhibitor (SNRI) that has demonstrated efficacy in the treatment of depression, generalized anxiety disorder, social anxiety disorder, and panic disorder. Two large-scale, double-blind, randomized, parallel-group, placebo-controlled trials have also demonstrated that venlafaxine ER is more effective than placebo in the treatment of PTSD.[24,25] In addition, the efficacy of venlafaxine ER treatment in PTSD has been found to be at least comparable to that of sertraline, an agent with established efficacy and an approved indication for the treatment of PTSD.[25] Moreover, evidence from a pooled analysis by Thase and colleagues[26] suggests that in the treatment of MDD, the efficacy of venlafaxine, but not SSRIs, is unaffected by gender or age.

The purpose of this study was to examine the effects of trauma type and gender on responsiveness to treatment with venlafaxine ER in patients with PTSD using a relatively large sample of patients of both genders with diverse trauma types based on pooled data from 2 previous studies.[24,25]

METHOD

Analysis Population

Data were pooled from 2 flexible-dose, parallel-group, randomized, double-blind trials comprising 687 outpatients with a primary diagnosis of PTSD treated with venlafaxine ER (37.5 mg/day–300 mg/day) or placebo: a 12-week trial conducted in the United States (March 2001 to December 2002), which included a sertraline arm (N = 173) (not included in this report), and a placebo-controlled 24-week trial conducted in 12 countries outside the United States (October 2001 to December 2003).

Patient Sample

To be included in either study, patients had to be male or female outpatients aged ≥ 18 years with a primary diagnosis of DSM-IV PTSD and a score of at least 60 on the 17-item Clinician-Administered PTSD Scale abbreviated 1-week Symptom Status version (CAPS-SX-17)[27]; have had PTSD symptoms for at least the previous 6 months; have a negative serum pregnancy test at screening (for women of childbearing potential); be in generally good health as determined by the investigator on the basis of medical history, physical examination, and screening laboratory results; be willing and able to return for all protocol-defined visits; and be willing and able to provide written informed consent prior to admission. For the non-U.S. study, patients were required to be fluent in written and spoken forms of English, Spanish, or Portuguese.

Subjects were excluded if they had intolerance, hypersensitivity, or nonresponse to a previous adequate trial of venlafaxine or sertraline (in the U.S. trial); inability to tolerate or respond to previous adequate trials of 3 or more antidepressants; a current primary diagnosis of major depressive disorder or an anxiety disorder other than PTSD; a current mental disorder due to a general medical condition or history of bipolar disorder, schizophrenia, or other psychotic disorder; alcohol or drug abuse or dependence within 6 months of random assignment or a positive urine drug screen; a high risk of suicide or violence; used any investigational drug, antipsychotic, or monoamine oxidase inhibitor within 30 days of randomization; received electroconvulsive therapy (ECT) within 3 months of random assignment or were likely to require ECT during the study; used triptans or any other psychoactive drug or herbal preparation within 7 days of random assignment; had current involvement in criminal proceedings or compensation claims related to trauma; or if they were women

who were breastfeeding, pregnant, or sexually active without acceptable birth control. Subjects who had initiated or changed psychotherapy of any kind within 3 months of potential study enrollment were also excluded.

The research for the 12-week study was conducted at 59 psychiatric outpatient centers in the United States. The research for the 6-month study was conducted at 56 outpatient psychiatric clinic sites in Argentina, Chile, Colombia, Denmark, Finland, Mexico, Norway, Portugal, South Africa, Spain, Sweden, and the United Kingdom. Both studies were performed in accordance with the Declaration of Helsinki and its amendments and required written informed consent from all patients before study enrollment. The informed consent form, protocol, and amendments received independent ethics committee/institutional review board approval before the study began.

Study Design

Patients in each of the 2 trials combined in this analysis were enrolled by the site investigators. Following a washout period of at least 7 days, patients who met entry criteria were randomly assigned to double-blind, parallel treatment with venlafaxine ER or placebo, followed by a taper period of up to 2 weeks and poststudy evaluation (4–10 days after taper). Wyeth Research (Collegeville, Penn.) sent each site a table of computer-generated numbers randomized in blocks of 6, and patients were assigned packages linked to the randomization numbers in numerical order by the site investigator using the randomization tables. Investigators followed the protocol-specified medication dosing guidelines for venlafaxine ER (75 mg/day–300 mg/day, with a 4-day lead-in dose at baseline of 37.5 mg/day) and increased the dose to the next higher level based on tolerability for patients who did not achieve remission, which was operationally defined as a score less than or equal to 20 on the CAPS-SX-17, a cutoff that has been previously established.[28,29] In both studies, for patients not in remission, venlafaxine ER dosing was increased as tolerated to a maximum dose of 75 mg/day at day 5, 150 mg/day at day 14, 225 mg/day at day 28, and 300 mg/day at day 42. Study visits took place at baseline and at the end of study treatment weeks 1, 2, 4, 6, 8, and 12 in the 12-week study and additionally at weeks 18 and 24 for the 24-week study. In both studies, patients also underwent a follow-up visit or a visit at the time of discontinuation if the patient withdrew before the scheduled time of study completion.

For the international study, where necessary, the informed consent form and patient self-rating documents were translated into either Spanish or Portuguese by a U.S. agency and certified as accurate. Local affiliate medical directors confirmed the accuracy of each translation prior to use. Training and testing on the CAPS-SX-17 to ensure correct scoring using 1 or more videotaped patient interviews were provided to the principal investigator and to an additional rater for each site. All investigators were required to be fluent in English.

Trauma Categories and Types

The primary trauma types recorded for patients included accidental injury, combat, nonsexual abuse, adult sexual abuse, childhood sexual abuse, unexpected death, and other (unknown, witnessing, and natural disaster). Additionally, trauma types were aggregated into sexual/nonsexual and violent/nonviolent trauma categories. The trauma types in the sexual category included childhood sexual abuse and adult sexual abuse; those in the nonsexual category included combat, nonsexual abuse, accidental injury, natural disaster, witnessing, and unexpected death ("other" and "unknown" trauma types were not included in either category). The trauma types included in the violent category included combat, childhood sexual abuse, adult sexual abuse, and nonsexual abuse; those in the nonviolent category included accidental injury, natural disaster, witnessing, unexpected death ("other" and "unknown" trauma types were not included in either category).

Efficacy Assessments

The primary efficacy end point in this study was the mean CAPS-SX-17 score change from baseline in the intent-to-treat (ITT) population using the last-observation-carried-forward (LOCF) method. The CAPS-SX-17 assesses the 17 PTSD symptoms listed in the DSM-IV divided into the reexperiencing, avoidance/numbing, and hyperarousal symptom clusters. Secondary efficacy outcomes included changes from baseline to end point in CAPS-SX-17 symptom cluster scores and frequency of remission (CAPS-SX-17 score ≤ 20). Other secondary outcome measures included ratings from the clinician-administered Clinical Global Impressions-Severity of Illness (CGI-S) scale,[30] the 17-item Hamilton Rating Scale for Depression (HAM-D-17),[31] the patient-rated Connor-Davidson Resilience Scale[32] (CD-RISC), and the Sheehan Disability Scale (SDS).[33] The CD-RISC is a 25-item scale that asks the respondent to rate the extent to which he or she agrees with each of a series of items measuring resilience over the past month on a scale of 0 to 4 (with 0 indicating "never" and 4 indicating "all of the time"). The SDS is a 3-item scale that evaluates the extent to which PTSD symptoms have disrupted patients' work/school schedule, social life, and family life/home responsibilities. The CGI-S, HAM-D-17, and SDS were measured at baseline and weeks 2, 4, 6, 8, and 12; the CD-RISC was measured at baseline and weeks 4 and 12.

Safety Assessments

Adverse events and use of concomitant treatments were recorded at all visits. Safety measurements included

Table 1. Demographic and Baseline Characteristics Among Outpatients Treated With Venlafaxine ER or Placebo for PTSD

	US Study		International Study		Pooled	
Characteristic, N (%)	Venlafaxine ER (N = 179)	Placebo (N = 179)	Venlafaxine ER (N = 161)	Placebo (N = 168)	Venlafaxine ER (N = 340)	Placebo (N = 347)
Gender[a]						
Men	55 (30.7)	65 (36.3)	72 (44.7)	79 (47.0)	127 (37.3)	144 (41.5)
Women	124 (69.3)	114 (63.7)	89 (55.3)	89 (53.0)	213 (62.7)	203 (58.5)
Ethnicity[b]						
White	121 (67.6)	135 (75.4)	92 (57.1)	100 (59.5)	213 (62.7)	235 (67.7)
Black	36 (20.1)	21 (11. 7)	4 (2.5)	3 (1.8)	40 (11.8)	24 (6.9)
Asian	0 (0.0)	0 (0.0)	1 (0.6)	2 (1.2)	1 (0.3)	2 (0.6)
Hispanic	20 (11.2)	17 (9.5)	54 (33.5)	57 (34.0)	74 (21.8)	74 (21.3)
Other	2 (1.1)	6 (3.4)	10 (6.2)	6 (3.6)	12 (3.5)	12 (3.5)
Trauma type[b]						
Accidental injury	18 (10.1)	21 (11.7)	30 (18.6)	31 (18.5)	48 (14.1)	52 (15.0)
Combat	19 (10.6)	18 (10.1)	20 (12.4)	20 (11.9)	39 (11.5)	38 (11.0)
Nonsexual abuse	51 (28.5)	48 (26.8)	42 (26.1)	52 (31.0)	93 (27.4)	100 (28.8)
Sexual abuse (adult)	26 (14.5)	26 (14.5)	19 (11.8)	21 (12.5)	45 (13.2)	47 (13.5)
Sexual abuse (childhood)	28 (15.6)	28 (15.6)	2 (1.2)	1 (0.6)	30 (8.8)	29 (8.4)
Unexpected death	22 (12.3)	21 (11.7)	26 (16.2)	18 (10.7)	48 (14.1)	39 (11.2)
Other	15 (8.4)	17 (9.5)	22 (13.7)	25 (14.9)	37 (10.9)	42 (12.1)

[a]p = .0009 U.S. vs. international study.
[b]p < .0001 U.S. vs. international study.
Abbreviations: ER = extended release, PTSD = posttraumatic stress disorder.

weight at baseline and week 12 and resting pulse rate and 2 sitting blood pressure readings at all visits. Other evaluations included a physical examination at baseline; blood chemistry determinations, hematology, urinalysis, and urine toxicology at screening; and recording of last menstrual period for women of childbearing age.

Statistical Methods

Analyses of efficacy variables were performed on the ITT population (i.e., on all randomly assigned patients who had received at least 1 dose of study medication and had at least 1 postbaseline evaluation). The primary efficacy outcome was the change in the CAPS-SX-17 score from baseline to week 12. For patients who discontinued participation before study completion, the last postdose observed value was used for end point analysis (LOCF). In addition to the LOCF value, the observed changes at each visit were computed (but are not included in this report).

Differences in responsiveness to treatment were explored using analysis-of-covariance (ANCOVA) models to evaluate the effects of trauma type, age, gender, and age-by-gender interaction. Menopausal status was evaluated by stratifying patients by age ranges (≤ 40 years, > 40 to 54 years, > 54 years) to approximate premenopausal and postmenopausal status in women and to minimize the overlap between the premenopausal and postmenopausal groups. Comparisons were made between the youngest and oldest female groups.

The statistical model for hypothesis testing was ANCOVA on the change from baseline in CAPS-SX-17 score, with baseline score as covariate and factors for treatment group, patient group (gender or trauma type in separate models), and, in models evaluating menopausal status, interactions of treatment, and patient group and treatment, gender, and age group. All inferential tests were 2-tailed main effects and were tested at the $\alpha = .05$ level of significance. Interactions were tested at the higher α level of .10 because of the reduced statistical power for interaction tests in ANCOVA. The continuous secondary efficacy end points were analyzed by the same method as the primary end point. No adjustment was made for multiple analyses. Categorical variables, such as the frequency of remission, were analyzed using χ^2 tests. Version 9 of the SAS system (SAS Inc, Cary, N.C.) was used for all statistical analyses.

RESULTS

Demographic and Baseline Clinical Characteristics

As shown in Table 1, the ITT population consisted of 687 outpatients with a primary diagnosis of PTSD who were treated with venlafaxine ER (37.5 mg/day to 300 mg/day) or placebo: 340 patients received venlafaxine ER (127 men, 213 women), and 347 patients received placebo (144 men, 203 women). Of these, 501 patients completed the 12 weeks of double-blind treatment used for all efficacy analyses: 242 patients in the venlafaxine ER group and 249 patients in the placebo group.

Although there were statistically significant ($p < .001$) differences in demographic and baseline clinical characteristics between the studies used for the pooled analysis, there were no statistically significant differences between the venlafaxine ER and placebo groups within a study or in the pooled study population, including in

Table 2. Selected Measures of Illness Severity at Baseline Among Outpatients Treated With Venlafaxine ER or Placebo for PTSD

	US Study				International Study				Pooled			
	Venlafaxine ER (N = 179)		Placebo (N = 179)		Venlafaxine ER (N = 161)		Placebo (N = 168)		Venlafaxine ER (N = 340)		Placebo (N = 347)	
Measure	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
CAPS-SX-17 total score												
Women	83.20	14.00	80.75	14.88	80.49	14.81	83.55	15.61	82.07	14.37	81.98	15.23
Men	85.71	16.98	82.98	14.28	81.71	14.46	82.14	15.44	83.44	15.66	82.52	14.88
Total	84.16	14.81	81.40	14.51	80.09	13.66	84.75	15.23	82.29	14.50	82.70	15.00
CAPS-SX-17 cluster B score												
Women	23.99	6.10	22.54	6.96	24.79	5.78	25.16	6.64	24.32	5.97	23.68	6.93
Men	22.95	7.41	22.65	6.05	24.46	6.16	24.62	6.79	23.80	6.74	23.73	6.52
Total	23.84	6.47	22.50	6.50	23.98	6.54	26.13	6.60	24.08	6.22	23.90	6.79
CAPS-SX-17 cluster C score												
Women	33.59	7.92	33.08	8.31	31.39	7.87	33.46	7.39	32.67	7.96	33.25	7.90
Men	36.24	8.42	34.74	7.27	32.35	8.19	32.18	8.06	34.03	8.48	33.34	7.79
Total	34.43	8.08	33.33	8.01	31.67	7.57	33.04	7.47	33.07	8.23	33.49	7.85
CAPS-SX-17 cluster D score												
Women	25.62	4.93	25.13	5.94	24.31	6.32	24.93	5.80	25.08	5.58	25.04	5.86
Men	26.53	5.97	25.60	5.84	24.90	4.89	25.32	5.57	25.61	5.42	25.44	5.67
Total	25.88	5.14	25.57	5.66	24.44	5.63	25.58	5.55	25.14	5.29	25.31	5.69
CD-RISC score												
Women	56.34	16.28	53.63	16.71	56.77	17.50	51.49	17.29	56.52	16.76	52.69	16.96
Men	53.96	17.94	55.16	15.54	54.41	19.56	54.76	17.22	54.22	18.81	54.94	16.42
Total	55.83	17.22	54.46	16.23	56.66	17.53	53.72	16.44	56.10	17.64	52.71	16.70
HAM-D-17 score												
Women	18.24	6.26	17.43	5.49	17.97	7.15	16.60	6.81	18.13	6.63	17.06	6.10
Men	17.71	6.41	16.40	5.22	16.38	5.82	15.58	5.84	16.95	6.10	15.95	5.56
Total	18.15	6.20	17.09	5.30	16.67	6.24	17.52	6.16	17.52	6.43	16.86	5.72
CGI-S score												
Women	4.64	0.77	4.61	0.70	4.71	0.73	4.66	0.67	4.67	0.75	4.63	0.69
Men	4.73	0.71	4.54	0.79	4.64	0.81	4.72	0.82	4.68	0.77	4.64	0.81
Total	4.66	0.72	4.55	0.70	4.67	0.75	4.74	0.72	4.68	0.75	4.62	0.74
SDS score												
Women	19.20	7.32	18.26	6.20	20.06	5.74	19.51	6.15	19.56	6.71	18.81	6.20
Men	18.52	7.65	17.06	6.78	18.36	6.81	18.94	6.41	18.43	7.15	18.09	6.63
Total	18.80	7.38	17.90	6.56	18.39	5.35	20.15	6.03	18.73	6.83	18.59	6.32

Abbreviations: CAPS-SX-17 = 17-item Clinician-Administered PTSD Scale abbreviated 1-week Symptom Status version, CD-RISC = Connor-Davidson Resilience Scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, ER = extended release, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, PTSD = posttraumatic stress disorder, SDS = Sheehan Disability Scale.

Table 3. Prescribed Dosing at the Final Visit (week 12)

	US Study[a]		International Study[b]		Pooled	
Dose	LOCF (N = 179)	Completers (N = 118)	LOCF (N = 161)	Completers (N = 124)	LOCF (N = 340)	Completers (N = 242)
Average mean dose, mg/d	199.8	217.8	207.9	232.9	203.6	225.5
Maximum mean dose, mg/d	224.6	241.8	221.5	245.0	223.1	243.4

[a]Week 12 of 12-week study.
[b]Week 12 of 24-week study.
Abbreviation: LOCF = last observation carried forward.

trauma type (Table 1), in clinical characteristics (Table 2), or in the proportion of patients who completed the study.

The mean daily dose of venlafaxine ER at the week 12 end point was 203.6 mg/day, and the mean maximum protocol-specified dose level was 223.1 mg/day for the pooled studies (Table 3).

Efficacy Analysis

The primary end point, change in CAPS-SX-17 score in response to treatment at week 12 (LOCF), is shown for each trauma type in Table 4. The change in the primary and secondary outcome measures analyzed by protocol, baseline severity, treatment, and trauma type using ANCOVA are shown in Table 5. It can be seen that baseline severity and treatment showed statistically significant associations with response on all reported outcome measures, while the effects of trauma type were significant only for the CD-RISC and SDS, and effects of protocol were significant for CAPS-SX-17 total and cluster C and D scores and for CGI-S and HAM-D-17 total scores.

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Table 4. Change in CAPS-SX-17 Score in Response to Treatment by Trauma Type

	Venlafaxine ER (N = 340)			Placebo (N = 347)		
Trauma Type, mean ± SD	Baseline	Week 12	Difference	Baseline	Week 12	Difference
Accidental injury	77.75 ± 14.45	39.17 ± 27.73	–38.58 ± 24.38	81.25 ± 13.80	42.61 ± 31.34	–38.35 ± 31.70
Combat	86.79 ± 12.90	52.72 ± 34.34	–34.06 ± 29.51	83.55 ± 13.98	47.92 ± 25.08	–34.58 ± 26.49
Nonsexual abuse	84.32 ± l5.14	34.58 ± 28.63	–49.59 ± 29.11	80.36 ± 13.80	44.77 ± 32.04	–34.79 ± 28.93
Sexual abuse (adult)	85.56 ± 15.65	38.16 ± 31.53	–47.40 ± 27.75	86.36 ± 19.68	46.18 ± 25.69	–38.59 ± 24.52
Sexual abuse (childhood)	80.33 ± 13.90	40.69 ± 25.32	–40.00 ± 20.90	86.79 ± 16.18	53.56 ± 36.24	–32.74 ± 30.09
Unexpected death	81.02 ± 15.41	36.19 ± 29.08	–44.49 ± 25.95	77.92 ± 13.93	41.51 ± 25.37	–36.4l ± 24.60
Other	80.27 ± 14.07	29.91 ± 20.58	–50.44 ± 24.22	82.69 ± l3.62	48.78 ± 26.81	–33.60 ± 28.50

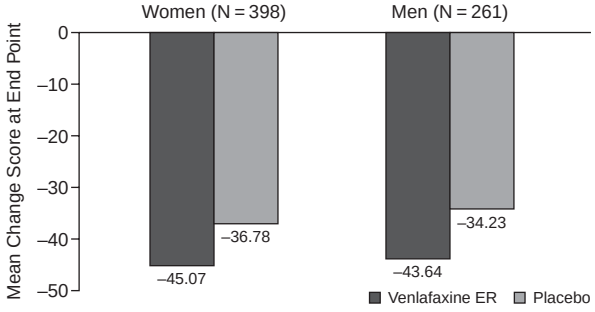
Abbreviations: CAPS-SX-17 = 17-item Clinician-Administered PTSD Scale abbreviated 1-week Symptom Status version, ER = extended release.

Table 5. Significance of Predictors at End Point[a]

Predictor/Outcome	Protocol[b]	Baseline Severity	Treatment[c]	Trauma Type[d]	Treatment-By-Trauma-Type Interaction
CAPS-SX-17 total score	.0235	.0001	.0005	.2771	.2151
CAPS-SX-17 cluster B score	.1610	< .0001	.0037	.2751	.6546
CAPS-SX-17 cluster C score	.0246	< .0001	.0015	.3349	.1424
CAPS-SX-17 cluster D score	.0313	< .0001	.0010	.2277	.1524
CD-RISC score	.8813	< .0001	.0121	.0012	.7490
CGI-S score	.0396	< .0001	.0003	.2169	.0278
SDS score	.7675	< .0001	.0005	.0057	.1319
HAM-D-17 total score	< .0001	< .0001	.0006	.0625	.0392

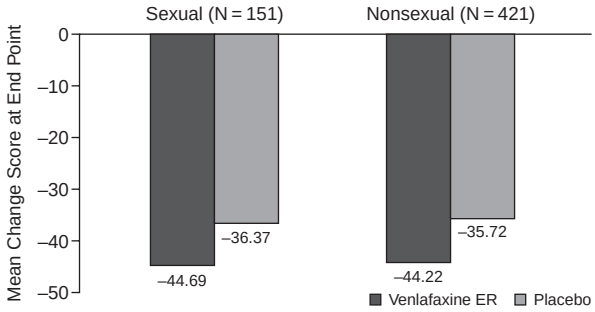
[a]Week 12 (last observation carried forward).
[b]U.S. study or international study.
[c]Venlafaxine ER or placebo.
[d]Accidental injury, nonsexual abuse, sexual abuse (adult), sexual abuse (childhood), unexpected death, or other.
Abbreviations: CAPS-SX-17 = 17-item Clinician-Administered PTSD Scale abbreviated 1-week Symptom Status version, CD-RISC = Connor-Davidson Resilience Scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, ER = extended release, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, SDS = Sheehan Disability Scale.

Figure 1. CAPS-SX-17 Score Change Following 12 Weeks of Treatment (LOCF)[a]



[a]Analysis of covariance using LOCF scores for the intent-to-treat population. Greater score change indicates greater improvement. Effect of treatment was significant ($p \leq .05$). Effect of gender on mean change score from baseline was not significant. Treatment-by-gender interaction was not significant.
Abbreviations: CAPS-SX-17 = 17-item Clinician-Administered PTSD Scale abbreviated 1-week Symptom Status version, ER = extended release, LOCF = last observation carried forward.

Figure 2. Response to Treatment in Patients With Sexual Versus Nonsexual Trauma (CAPS-SX-17)[a]

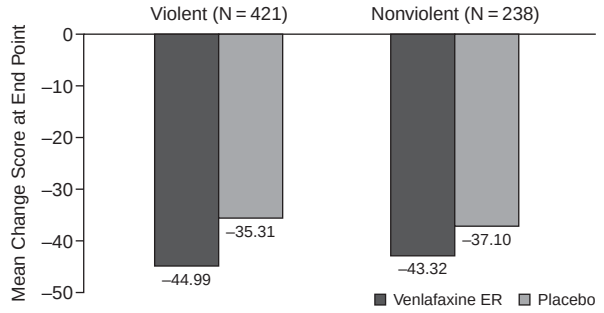


[a]Analysis of covariance using last-observation-carried-forward scores for the intent-to-treat population. Greater score change indicates greater improvement. Effect of treatment was significant ($p \leq .05$). Effects of trauma category and the treatment-by-trauma category interaction were not significant.
Abbreviations: CAPS-SX-17 = 17-item Clinician-Administered PTSD Scale abbreviated 1-week Symptom Status version, ER = extended release.

As depicted in Figure 1, neither the difference by gender in CAPS-SX-17 response (defined as the mean total score change from baseline to end point), nor the treatment-by-gender interaction was statistically significant.

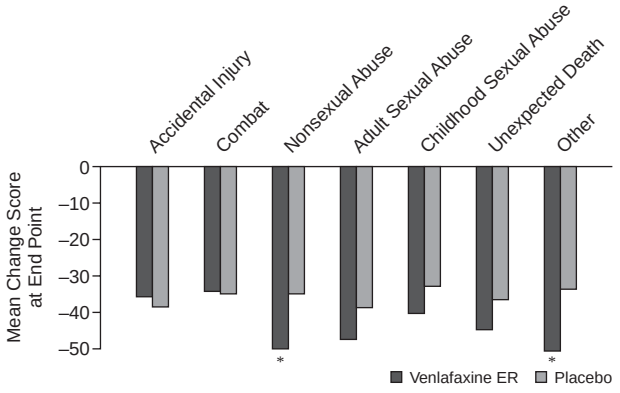
Based on the aggregation of conceptually related trauma types, neither the difference in CAPS-SX-17 response between sexual (childhood sexual abuse or adult sexual abuse) and nonsexual trauma (combat, nonsexual abuse, accidental injury, natural disaster, witnessing, or unexpected death) categories shown in Figure 2, nor the difference between violent (combat, childhood sexual abuse, adult sexual abuse, or nonsexual abuse) and nonviolent (accidental injury, natural disaster, witnessing, or

Figure 3. Response to Treatment in Patients With Violent Versus Nonviolent Trauma (CAPS-SX-17)[a]



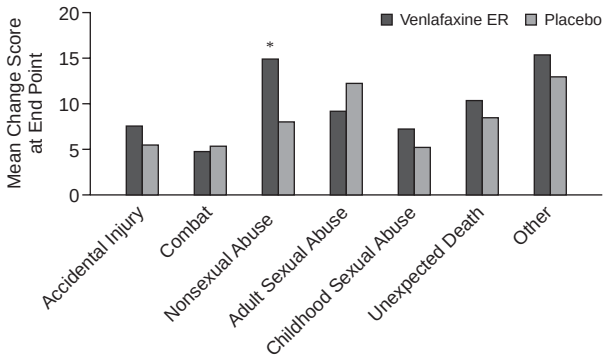
[a]Analysis of covariance using last-observation-carried-forward scores for the intent-to-treat population. Greater score change indicates greater improvement. Effect of treatment was significant ($p \leq .05$). Effects of trauma category and the treatment-by-trauma category interaction were not significant.
Abbreviations: CAPS-SX-17 = 17-item Clinician-Administered PTSD Scale abbreviated 1-week Symptom Status version, ER = extended release.

Figure 4. Response to Treatment in Patients by Trauma Type (CAPS-SX-17)[a]



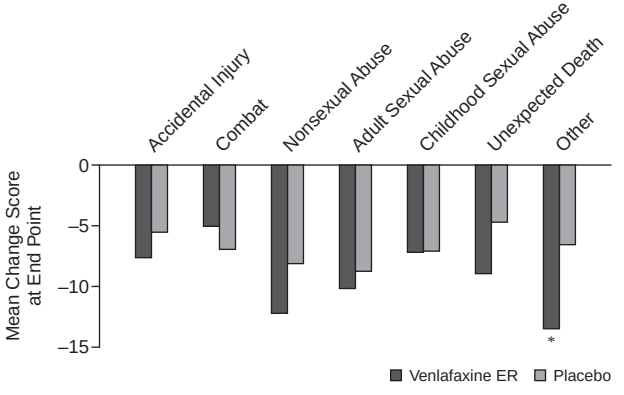
[a]Analysis of covariance using last-observation-carried-forward scores for the intent-to-treat population. Greater score change indicates greater improvement. Effect of treatment was significant ($p \leq .05$). Effects of trauma type and the treatment-by-trauma-type interaction were not significant.
*$p \leq .05$ venlafaxine ER vs. placebo.
Abbreviations: CAPS-SX-17 = 17-item Clinician-Administered PTSD Scale abbreviated 1-week Symptom Status version, ER = extended release.

Figure 5. CD-RISC Score Change in Patients by Trauma Type[a]



[a]Analysis of covariance using last-observation-carried-forward scores for the intent-to-treat population. Greater score change indicates greater improvement. Effect of treatment was significant ($p \leq .05$). Effect of trauma type was significant ($p = .0012$); the treatment-by-trauma-type interaction was not significant.
*$p \leq .05$ venlafaxine ER vs. placebo.
Abbreviations: CD-RISC = Connor-Davidson Resilience Scale, ER = extended release.

Figure 6. SDS Score Change in Patients by Trauma Type[a]



[a]Analysis of covariance using last-observation-carried-forward scores for the intent-to-treat population. Greater score change indicates greater improvement. Effect of treatment was significant ($p \leq .05$). Effect of trauma type was significant ($p = .0057$); the treatment-by-trauma-type interaction was not significant.
*$p \leq .05$ venlafaxine ER vs. placebo.
Abbreviations: ER = extended release, SDS = Sheehan Disability Scale.

unexpected death) trauma categories shown in Figure 3 was statistically significant. Additionally, the treatment-by-trauma category interaction was not statistically significant in either case.

Response to treatment was also analyzed by individual trauma type (accidental injury, combat, nonsexual abuse, adult sexual abuse, childhood sexual abuse, unexpected death, and other [unknown, witnessing, and natural disaster]). As shown in Figure 4, differences between patients in CAPS-SX-17 response to treatment-by-trauma type were not statistically significant. Figure 5 shows, however, that the CD-RISC score change at end point was significantly different between trauma types, although the treatment-by-trauma-type interaction was not. Likewise, Figure 6 shows that the SDS score change was significantly different between trauma types, although the treatment-by-trauma-type interaction was not. Figure 7 shows that the HAM-D-17 score change nearly reached

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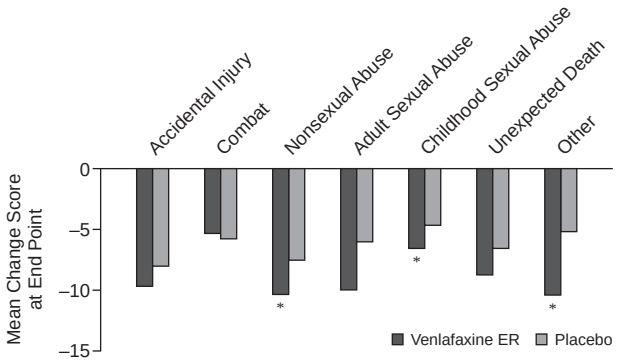
Figure 7. HAM-D-17 Score Change in Patients by Trauma Type[a]



[a]Analysis of covariance using last-observation-carried-forward scores for the intent-to-treat population. Greater score change indicates greater improvement. Effect of treatment was significant ($p \leq .05$). Effect of trauma type was nearly significant ($p = .0625$); the treatment-by-trauma-type interaction was significant ($p = .0392$).
*$p \leq .05$ venlafaxine ER vs. placebo.
Abbreviations: ER = extended release, HAM-D-17 = 17-item Hamilton Rating Scale for Depression.

Table 6. Change in CAPS-SX-17 Scores at End Point by Age, Gender, and Treatment

	≤ 40 y		> 40 to 54 y		> 54 y	
Variable	N	Mean (SD) Change	N	Mean (SD) Change	N	Mean (SD) Change
Venlafaxine ER						
Women	95	–43.0 (26.6)	78	–50.1 (27.9)	33	–39.2 (27.5)
Men	45	–46.6 (29.7)	46	–40.4 (24.5)	29	–44.1 (25.2)
Placebo						
Women	98	–35.7 (28.9)	68	–38.5 (29.6)	26	–36.1 (27.4)
Men	60	–42.5 (27.5)	43	–31.0 (23.7)	38	–24.9 (25.7)

Abbreviations: CAPS-SX-17 = 17-item Clinician-Administered PTSD Scale abbreviated 1-week Symptom Status version, ER = extended release.

statistical significance ($p = .0625$) but that the treatment-by-trauma-type interaction was statistically significant ($p = .0392$). The effect of trauma type on CGI-S score change was not significant (Table 5), but the treatment-by-trauma-type interaction for the CGI-S was significant ($p = .0278$).

Treatment effects on both the HAM-D-17 and CGI-S tended to be consistently smaller in patients with combat-related trauma than in patients with other types of trauma. Of individual trauma types, nonsexual abuse affected both resilience and disability, with patients who had experienced nonsexual abuse showing a trend toward better response on resilience and disability than those who had experienced sexual abuse.

Table 6 shows changes in CAPS-SX-17 scores at end point by age (≤ 40 years, > 40 to 54 years, and > 54 years), gender, and treatment, with age categories in women chosen to approximate premenopausal and postmenopausal status. No significant treatment-by-age, treatment-by-gender, age-by-gender, or treatment-by-age-by-gender interactions were detected; however, a significant effect was found for treatment ($p = .0009$) as well as for gender ($p = .0354$).

DISCUSSION

Changes in the primary outcome measure, the CAPS-SX-17 total score, and in all CAPS-SX-17 cluster scores following 12 weeks of treatment were significantly greater for the venlafaxine ER group than for the placebo group in the ITT population (LOCF) for both men and women (i.e., there were no significant effects of gender or the gender-by-treatment interaction). The analysis of treatment responsiveness by age and gender to evaluate the effect of menopausal status on treatment response using the lowest and highest age groups (≤ 40 and > 54 years, respectively) to approximate premenopausal and postmenopausal status, respectively, in women showed no significant effect of age and no significant age-by-treatment interaction.

In general, venlafaxine ER showed greater efficacy than placebo across the individual trauma types and outcome measures evaluated, and in each case, showed a significant main effect for treatment. Individual trauma type did not significantly affect treatment response as measured by change from baseline to end point in the CAPS-SX-17 total or cluster scores. Change from baseline to end point on the employed measure of disability (SDS), however, was significantly affected by individual trauma type as was resilience (CD-RISC), with depression (HAM-D-17) almost reaching statistical significance.

There were no significant differences across trauma type between the venlafaxine ER and placebo groups in baseline-to-end point change scores for the CAPS-SX-17, CD-RISC, HAM-D-17, or SDS with the exception of the nonsexual abuse trauma type for the CAPS-SX-17, which showed a significant difference in treatment effect (venlafaxine ER = –49.59, placebo = –34.79); this is consistent with previous data showing the serious long-term sequelae of early sexual abuse[34,35] and with the suggested appropriateness of combined pharmacotherapy and psychotherapy in such cases.[13] Because patients who have experienced nonsexual abuse may be less treatment resistant than those who have experienced sexual abuse, they may as a group show a more favorable response to active treatment than placebo relative to their sexually abused counterparts. Effect of trauma type was significant for resilience (CD-RISC) and disability (SDS) and nearly significant for depression (HAM-D-17). There was a statistically significant treatment-by-trauma-type interaction for HAM-D-17 depression. For these outcome measures, treatment effects tended to be smaller in the combat-

related trauma type than in other types of trauma. This result is consistent with the findings from several studies that have reported smaller effects of interventions, both pharmacologic[19,21,36] and psychotherapeutic,[37,38] in combat veterans as compared with other trauma populations.

To increase statistical power, trauma types were aggregated into sexual/nonsexual and violent/nonviolent trauma categories. These groupings are of particular interest given the finding that rape has been found to be much more frequent among women than men and, along with combat, is associated with the highest prevalence of PTSD and that women are at considerably higher risk of experiencing PTSD in response to physical assault than are men. In both instances, the effect of treatment was statistically significant, but there was no statistically significant effect of sexual/nonsexual trauma category or violent/nonviolent trauma category on response to treatment as assessed by the primary outcome measure, baseline-to-end point change in CAPS-SX-17 score, or the interaction of either trauma category classification with treatment.

Limitations of the present analysis are that it did not evaluate the effect of the number of exposures to the primary trauma, history of other traumas, age at which traumas occurred, or how recently prior to the study traumas occurred. The number and severity of traumatic events have been related to the severity of PTSD symptomatology,[39] with multiple events having a stronger effect than a single previous event.[40] Moreover, individuals who experience multiple events involving assaultive violence in childhood have been found to be more likely to experience PTSD from trauma in adulthood.[40] This study also did not evaluate the effects of comorbidities such as depression or other anxiety disorders. Because certain trauma types, such as witnessing, natural disaster, and unknown trauma, occurred infrequently, they were combined into a category termed *other*. Moreover, the types of trauma were defined relatively broadly, encompassing experiences that were, in many respects, dissimilar (e.g., the type of combat may have involved direct physical injury, witnessing the injury or death of a friend or comrade, or shell shock; the trauma may have involved a discrete event or the accumulation of repeated exposures to a traumatic stressor such as artillery fire). For a number of study measures for certain trauma types, including the CAPS-SX-17 response for accidental injury and combat trauma types as well as the CD-RISC response for adult sexual abuse trauma, there was a large placebo effect, although the difference between placebo and venlafaxine ER treatment was not statistically significant. A placebo effect has been observed in other studies[41–43] and may be due in part to study patients' interactions with and/or a feeling of effectiveness resulting from involvement with the study investigators and staff. However, it is possible that these differences reflect a relatively small effect of venlafaxine ER in patients with these particular types of trauma. The sample size, while large relative to many randomized controlled trials, was still small given that the patient sample was broken down into 7 trauma types and that analyses were further subdivided by gender. Furthermore, in the analysis by age, gender, and treatment to evaluate the effect of menopause on responsiveness to treatment in women, the sample was further broken down by age group (with considerably fewer patients in the oldest group). In addition, a substantial number of women in the youngest group (≤ 40 years) may have been perimenopausal or even postmenopausal. The duration of pharmacotherapy was only 12 weeks, which is relatively short for treatment of PTSD, possibly minimizing differences between subgroups that may have become apparent with longer-term treatment.

CONCLUSION

Overall, we did not find a significant gender effect associated with venlafaxine ER treatment of PTSD even when menopausal status was taken into account by comparing women in younger (≤ 40 years) and older (> 54 years) age groups. There may, however, still have been a substantial proportion of women in the younger age group who were perimenopausal or postmenopausal, and the sample size may have been too small to detect a difference by menopausal status. Ideally, studies assessing gender effects should categorize women by assessed menopausal status rather than by age. If such data are not available, analyses should employ an even greater separation between age groups to minimize overlap in menopausal status between younger and older women.

Future studies would benefit from analyses based on larger sample sizes; consideration of additional factors, such as age at the time of exposure to trauma and onset of PTSD and measures of quality of life outcomes in addition to symptom reports; chronicity of the illness and how recently before study entry the index trauma occurred; better characterization of differences between different types and categories of trauma, such as whether trauma occurs in response to a discrete event or repetition of any event or circumstances over a period of time; and consideration of whether the trauma involves harm or the threat of harm to oneself or someone else. Despite its limitations, our analysis found that trauma type influenced treatment outcome, although the effect was not consistent across clinical rating scales and seemed to affect domains such as disability and resilience more than core PTSD symptoms measured by CAPS-SX-17 total and cluster scores. There was also some suggestion in this study that PTSD associated with sexual abuse may be associated with less improvement in resilience and that PTSD associated with combat may be associated with less improvement in disability in response to pharmacotherapy than other types of trauma, although in both cases, further research is needed to determine whether such differences exist.

Drug names: sertraline (Zoloft and others), venlafaxine (Effexor and others).

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