Randomized, Double-Blind Comparison of Sertraline and Placebo for Posttraumatic Stress Disorder in a Department of Veterans Affairs Setting

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Objective: To evaluate the efficacy of sertraline in the treatment of posttraumatic stress disorder (PTSD) in a Veterans Affairs (VA) clinic setting involving patients with predominantly combat-related PTSD.

Method: 169 outpatient subjects with a DSM-III-R diagnosis of PTSD and who scored 50 or higher on Part 2 of the Clinician-Administered PTSD Scale (CAPS-2) at the end of a 1-week placebo run-in period participated. Patients recruited from 10 VA medical centers were randomly assigned to 12 weeks of flexibly dosed sertraline (25–200 mg/day) (N = 86; 70% with combat-related PTSD; 79% male) or placebo (N = 83; 72% combat-related PTSD; 81% male) between May 1994 and September 1996. The primary efficacy measures were the mean change in CAPS-2 total severity score from baseline to endpoint, in the total score from the Impact of Event Scale, and in the Clinical Global Impressions-Severity of Illness and Improvement scales.

Results: There were no significant differences between sertraline and placebo on any of the primary or secondary efficacy measures at endpoint. In order to understand the results, gender, duration of illness, severity of illness, type of trauma, and history of alcohol/substance abuse were explored as potential moderators of outcome, but no consistent effects were uncovered. Sertraline was well tolerated, with 13% of patients discontinuing due to adverse events.

Conclusion: Sertraline was not demonstrated to be efficacious in the treatment of PTSD in the VA clinic settings studied.

(J Clin Psychiatry 2007;68:711–720)

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Supported by funding from Pfizer Inc.

Acknowledgments are listed at the end of this article.

Statements of the authors do not reflect official policy or opinions of the U.S. Department of Veterans Affairs.

Dr. Baker is a stock shareholder of Pfizer and was a site investigator on the project that produced data for this manuscript. Dr. Sikes is an employee and Dr. Farfel is a former employee of Pfizer Inc. Drs. Friedman and Marmar report no additional financial or other relationships relevant to the subject of this article.

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Posttraumatic stress disorder (PTSD) has a lifetime prevalence in the United States in the range of 7% to 12%, with women affected twice as often as men.[1–3] Research has documented that PTSD is typically chronic, with a mean duration of 20 years, and is associated with a high degree of psychosocial and occupational impairment and elevated suicide rates.[4–6]

Advances in the treatment of PTSD have accelerated in recent years, with both psychosocial treatments and newer psychopharmacologic agents showing efficacy in controlled trials. Although some early studies supported the efficacy of some tricyclic antidepressants[7,8] and monoamine oxidase inhibitors[8] in the treatment of PTSD, selective serotonin reuptake inhibitors (SSRIs) are now the recommended treatment of choice.[9–11] Sertraline has been found to be efficacious in 2 large multicenter placebo-controlled trials in civilian populations,[12,13] as has paroxetine.[14,15] Response to these agents is not always evident in the short-term: one study found that when treatment with sertraline was extended from 12 to 36 weeks, 55% of nonresponding patients subsequently demonstrated a clinical response.[16] Moreover, discontinuation of SSRI treatment increased the odds of relapse.[13,17,18] Both sertraline (for short- and long-term treatment) and paroxetine

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(for short-term treatment) are now approved by the U.S. Food and Drug Administration for the treatment of PTSD.

In addition to these 2 SSRIs, fluoxetine was found to be better than placebo in 1 large study and 2 smaller studies.[19–21] Open-label studies with fluvoxamine[22–25] and citalopram[26] have suggested that these agents may also be promising. Dual-action drugs such as mirtazapine and nefazodone have also yielded some positive results in small preliminary trials, but results have not been confirmed with larger studies.[27–29] Promising results from other medications, including prazosin (an α_1 antagonist),[30] D-cycloserine (a partial *N*-methyl-D-aspartate receptor agonist)[31] and venlafaxine[32,33] have also been reported. Atypical antipsychotics have also shown usefulness as adjunctive agents in the treatment of PTSD.[34,35]

Most of the studies cited above were conducted in civilian populations, in which the number of women exceeded the number of men and the primary traumatic stressors included sexual or physical assault, motor vehicle accidents, and childhood abuse, among others. In contrast to those studies that showed consistent utility for SSRI pharmacotherapy in the treatment of PTSD, studies of pharmacologic treatments for combat-related PTSD, and especially those involving Vietnam veterans seeking treatment in Department of Veterans Affairs (VA) hospital treatment settings, have shown mixed results. Phenelzine demonstrated clear evidence of efficacy in a placebo-controlled trial with combat-related PTSD.[8] In a small (N = 12) 12-week study involving severe, combat-related PTSD, fluoxetine was not better than placebo.[36] Another study of fluoxetine involving both veterans and nonveterans with PTSD reported a much better treatment response among the nonveterans.[20] Because of the relatively poor response to monotherapies in the treatment of combat-related PTSD, combined approaches have also been tried. In a study of PTSD in combat veterans, the use of adjunctive risperidone (in addition to antidepressants and other medications) produced modest superiority to placebo on a scale of positive and negative symptoms associated with psychotic disorders, but no difference on a measure of PTSD symptoms.[35]

Several articles have reported mixed results from open trials evaluating SSRIs to treat combat-related PTSD.[22,24] More recent studies, however, have found that veterans recruited from the general population (rather than from VA hospital treatment settings) exhibited as much benefit from SSRI treatment as did male and female nonveterans.[14,15] In addition, a study of fluoxetine that recruited primarily male veterans with PTSD, about half of whom had been exposed to trauma during recent (United Nations and NATO) military conflicts, had positive results.[19]

A number of potentially confounding factors should be addressed in sorting out the efficacy of treatments for PTSD in VA settings. As mentioned, PTSD occurs at a substantially higher rate in women than men, despite increased rates of exposure among men both to individual and to multiple traumas.[1,3,37–39] However, PTSD studies in VA settings have tended to include predominantly (or exclusively) male military veterans exposed to combat-related traumas.[20,24,40] Furthermore, many male patients remaining in VA settings have an especially long duration of illness and have failed to respond to a number of treatment approaches. Indeed, it has been suggested that the apparent "treatment resistance" of VA patients may reflect the influences of chronicity and complex comorbidity including substance use disorders rather than a specific difference between combat- versus civilian-related PTSD.[41] No studies to date have examined the role of these variables as moderators of treatment outcome within a VA PTSD population.

The purpose of the current study was to evaluate the efficacy and safety of sertraline compared with placebo for subjects with predominantly combat-related PTSD seeking treatment in VA settings. A secondary goal was to examine several potential moderator variables in relation to efficacy.

METHOD

Study Design

This was a 12-week, double-blind, randomized comparison of flexibly dosed sertraline and placebo in the treatment of PTSD. The study was conducted at outpatient psychiatric clinics at 10 VA medical centers in the United States between May 1994 and September 1996. All patients who were screened as meeting eligibility criteria for the study were placed on a 1-week single-blind placebo pill washout during which baseline assessments were performed. Following the placebo run-in period, subjects were randomly assigned to either sertraline or matching placebo for 12 weeks of double-blind treatment. Randomization was performed centrally using a computer-generated randomization scheme.

Dosing of sertraline was flexible. Subjects who were assigned to sertraline received 25 mg/day for 1 week. Subjects who did not experience dose-limiting adverse events due to medication were increased to 50 mg/day in week 2. Subjects who failed to respond satisfactorily to 50 mg/day could, in the absence of dose-limiting adverse events, have their dose titrated in weekly 50 mg increments to a maximum of 200 mg/day depending on the subjects' response to the drug.

The study was approved by local institutional review boards at all centers, and subjects were required to provide written informed consent after an explanation of the benefits and risks of the study. The study was conducted in accordance with Good Clinical Practice guidelines and with the ethical principles that have their origins in the Declaration of Helsinki.

Study Patients

One hundred sixty-nine outpatient subjects with a DSM-III-R diagnosis of PTSD participated in this study. The diagnosis of PTSD was determined by trained raters who administrated Part 1 of the Clinician-Administered PTSD Scale (CAPS-1).[42] A minimum 6-month duration of PTSD was required (exceeding the 1-month minimum required by DSM-III-R). In addition, subjects needed to have a total score of 50 or higher on Part 2 of the Clinician-Administered PTSD Scale (CAPS-2)[43] at the end of a 1-week placebo run-in period.

Subjects included literate male and female subjects 18 years of age and older who had a negative urine drug screen at screening on day 1 of the placebo run-in, who at study entry had a complete medical and psychiatric history and physical examination with no significant medical problems, and who had discontinued all other psychotropic medication (except chloral hydrate for sleep) prior to entry into the study. Subjects were also included if they were judged reliable for medication compliance and, if female, were practicing a medically acceptable method of contraception and had a negative serum β–human chorionic gonadotropin pregnancy test.

Excluded from the study were subjects with an organic mental disorder or who had a primary current diagnosis meeting DSM-III-R criteria for major depression single episode, dysthymic disorder, personality disorder from clusters other than cluster C, obsessive-compulsive disorder, generalized anxiety disorder, panic disorder, simple or social phobia, agoraphobia, anxiety disorder, or bipolar disorder. Subjects who had any current psychotic features or had a history of schizophrenia, delusional disorder, or psychotic disorder were excluded. Meeting criteria for any substance use disorder in the past 6 months was also an exclusion. Also excluded were subjects who were receiving concomitant psychotropic therapy of any type, who had therapy with any depot neuroleptic within 6 months, or who would be receiving behavior therapy during the study, as well as subjects with a history of nonresponse to adequate treatment and subjects who were taking drugs with a psychotropic component, neuroleptics, MAOIs, antidepressants, or hypnotics or anxiolytics in the previous 2 weeks (5 weeks for fluoxetine). Other exclusion criteria included history or evidence of malignancy or significant hematologic, endocrine, cardiovascular, renal, hepatic, neurologic, or gastrointestinal disease; a liver function test result greater than twice the upper limit of the normal range at screening; current impulse control problems; and current involvement in litigation for disability benefits or for damages related to the subject's disorder.

Primary Efficacy Measures

Subjects' progress was evaluated with a series of efficacy measures that were administered at double-blind treatment weeks 1, 2, 3, 4, 6, 8, 10, and 12. Primary efficacy measures included the mean change in the total severity score of the CAPS-2, the mean change in the total score from the Impact of Event Scale (IES),[44] and the mean change in the Clinical Global Impressions-Severity of Illness (CGI-S) and Improvement (CGI-I) scales.[45] The CAPS-2 is a 25-item scale that measures the 17 core symptoms of PTSD defined by the DSM-III-R on dimensions of frequency and severity, as well as 8 associated features such as survivor guilt, feelings of hopelessness, depression, and functional impairment. The total score for the CAPS-2 is a sum of the 17 core symptom items. The IES is a 15-item self-report scale consisting of 7 intrusion items and 8 avoidance items.

Secondary Efficacy Measures

The secondary outcome measures for this study consisted of the Davidson Trauma scale,[46] the 24-item Hamilton Rating Scale for Depression (HAM-D),[47] the Hamilton Rating Scale for Anxiety (HAM-A),[48] the Mississippi Rating Scale for Combat-Related PTSD–Civilian Trauma Version,[49,50] the Disorders of Extreme Stress–Not Otherwise Specified scale,[51] and the Pittsburgh Sleep Quality Index.[52] All secondary efficacy scales were administered at baseline and week 12 (or endpoint), with the exception of the Davidson Trauma Scale, which was completed by the subject at screening, at baseline, and at the end of weeks 1, 2, 3, 4, 6, 8, 10, and 12.

The Davidson Trauma Scale is a 17-item self-report scale that assesses frequency and severity of DSM-III-R–defined PTSD symptoms on separate 5-point scales. The Mississippi Rating Scale for Combat-Related PTSD–Civilian Trauma Version is a 39-item self-report scale that measures the current severity of 4 PTSD symptom dimensions: reexperiencing, withdrawal/numbing, arousal, and self-persecution. The Disorders of Extreme Stress–Not Otherwise Specified scale is a 39-item interviewer-completed scale assessing 7 categories of PTSD: regulation of affect and impulse, alterations in attention, alterations in self-perception, alterations in perceptions of a perpetrator, alterations in relations with others, somatization, and alterations in beliefs. Subjects rate whether or not the item was present in the past month. The Pittsburgh Sleep Quality Index assesses sleep impairment by asking the subject to report on his or her sleep habits and quality of sleep during the past month. Total scores were used for the Davidson Trauma Scale, Mississippi Rating Scale for Combat-Related PTSD–Civilian Trauma Version, Disorders of Extreme Stress–Not Otherwise Specified scale, and Pittsburgh Sleep Quality Index.

The CAPS-2 total score and the CGI-I scale were also used to define clinical response. On the CAPS-2, a response was defined a priori by a group of PTSD experts as a 30% or greater decrease in the total score, while on the CGI-I, the usual definition of a rating of 1 (very

much improved) or 2 (much improved) on clinical response was used.

Safety Assessments

Spontaneously reported adverse events were recorded throughout the study. A serious adverse event was defined as an event that occurred during the clinical trial that was fatal, life threatening, or potentially life threatening; resulted in permanent disability; required prolonged hospitalization; involved cancer or a congenital anomaly; was the result of a drug overdose; or suggested a significant hazard to the subject. The following safety measures were given to each subject in order to detect a potential adverse event: clinical laboratory tests (hematology test, blood chemistry test, urinalysis and microscopic examination, thyroid function evaluation, and serum β–human chorionic gonadotropin pregnancy test for women) at day 1 and at the end of weeks 6 and 12, a urine drug screen given at day 1 and at the end of weeks 6 and 8, and a physical examination that was performed on day 1 and at the end of week 12.

Statistical Analyses

Intent-to-treat efficacy analyses were conducted on endpoint data (week 12 for completers and at the last available visit for patients who did not complete the study) using all patients with at least 1 postbaseline assessment. Baseline comparability of the 2 treatment groups for demographic and clinical characteristics was assessed by analysis of variance for continuous variables and by the Cochran-Mantel-Haenszel test for categorical variables. Analysis of variance models included terms for treatment and center. The Cochran-Mantel-Haenszel tests included center as the stratification variable.

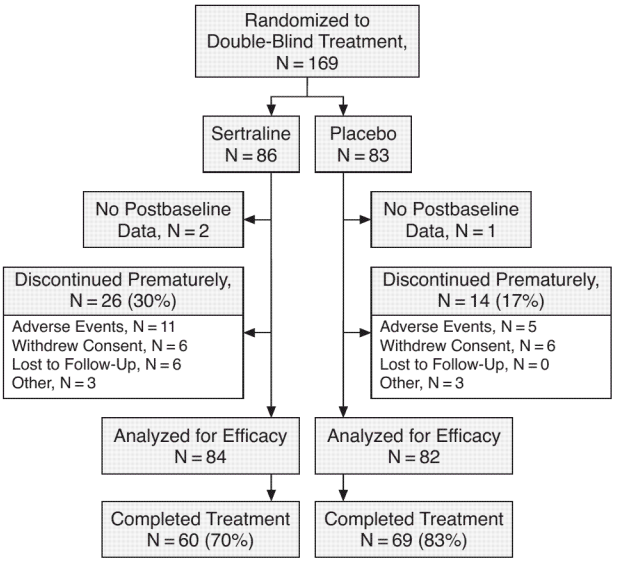
Efficacy analyses were performed using analysis of covariance for continuous variables for which a baseline measurement existed; for the CGI-I scale, an analysis of variance model was used. Responder rates were analyzed by the Cochran-Mantel-Haenszel test with center as the stratifying variable. Analysis of covariance models used change from baseline to endpoint as the dependent variable, and included treatment, center, and treatment-by-center interaction terms, with baseline measurement as the covariate. An additional secondary analysis was a mixed-effects linear model that examined relative differences between sertraline and placebo treatments in the rate of change (linear slope) from baseline to week 12 (or last value). All available data were used in this analysis. The models estimated fixed-effects for treatment and site, as well as the interactions of treatment with time. In addition, the models included a random intercept and a random slope. Treatment-by-site interactions were not significant and therefore not included in the models.

The role of several potential moderator variables, including gender, age, duration of illness, severity of illness (CAPS-2 score at baseline), type of trauma (combat vs. noncombat), and history of alcohol/substance abuse were examined in relation to sertraline efficacy for each of the 4 primary efficacy variables. Each variable was entered as a main effect covariate in the analysis of covariance/analysis of variance models described above, followed by entry of the covariate-by-treatment interaction term to test for differential relation to outcome for sertraline compared with placebo.

Safety analyses were performed using Fisher exact test for incidence of each individual adverse event and Cochran-Mantel-Haenszel test for proportion of subjects with adverse events and discontinuations. Adverse events were coded according to the World Health Organization dictionary. Safety analyses were performed for all patients that received at least 1 dose of study medication.

All statistical tests were 2-sided, and statistical significance was declared at the .05 α level.

Figure 1. Flowchart for Subjects Enrolled in Randomized, Double-Blind Comparison of Sertraline and Placebo for Posttraumatic Stress Disorder



RESULTS

Baseline Clinical and Demographic Characteristics

One hundred sixty-nine subjects (86 sertraline; 83 placebo) were randomly assigned to treatment and dispensed double-blind medication (Figure 1). All 169 subjects had follow-up safety data. The intent-to-treat population included 166 subjects, 84 who were treated with sertraline and 82 who were treated with placebo (2 sertraline and 1 placebo subject had no postbaseline efficacy data). One hundred twenty-nine subjects completed

Table 1. Demographic and Clinical Information on Posttraumatic Stress Disorder Patients by Gender

	Sertraline (N = 86)		Placebo (N = 83)	
Characteristic	Men (N = 68)	Women (N = 18)	Men (N = 67)	Women (N = 16)
Age, mean ± SD, y	46.8 ± 10.2	37.2 ± 10.4	47.8 ± 9.0	37.8 ± 8.4
Race, white, N (%)	44 (65)	14 (78)	47 (70)	15 (94)
Duration of illness, mean ± SD, y	19.7 ± 12.3	8.9 ± 7.3	20.9 ± 11.5	12.0 ± 11.9
Time from traumatic event, mean ± SD, y	24.0 ± 11.7	15.6 ± 12.4	25.9 ± 10.2	17.0 ± 13.4
Current major depression, N (%)	34 (50)	10 (56)	27 (40)	9 (56)
Current DSM-III-R anxiety disorder, N (%)	15 (22)	4 (22)	9 (13)	4 (25)
History of alcohol or substance abuse comorbidity, N (%)	40 (59)	6 (33)	41 (61)	4 (25)
Frequency of trauma by category, N (%)				
Serious accident, injury, or fire	3 (4.4)	0 (0)	0 (0)	0 (0)
Physical or sexual assault	2 (2.9)	12 (66.7)	2 (3.0)	10 (62.5)
Seeing someone hurt or die	3 (4.4)	2 (11.1)	6 (9.0)	3 (18.8)
Being in war or combat	58 (85.3)	2 (11.1)	59 (88.1)	1 (6.3)
Miscellaneous other events	2 (2.9)	2 (11.1)	0 (0)	2 (12.5)

Abbreviation: DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised.

the study: 60 (70%) in the sertraline group and 69 (83%) in the placebo group.

Baseline and clinical characteristics of the randomized sample broken down by gender are given in Table 1. Among women, there were no significant differences between sertraline and placebo groups on any of the baseline demographic or clinical characteristics. There were also no significant differences in these characteristics among men for sertraline versus placebo. Overall, the study sample was primarily male (sertraline: 79% [68/86]; placebo: 81% [67/83]) and white (67% vs. 75%, respectively). The mean age was 45 years (sertraline) and 46 years (placebo). The mean duration of illness in the sertraline group was 17 years with a mean time from traumatic event of 22 years; mean duration of illness was 19 years and mean time from traumatic event was 24 years in the placebo group. Collapsing across gender, there were no significant differences between the treatment groups in any of these baseline characteristics.

The most common traumatic event was being in war or combat, which occurred in 70% (60/86) of sertraline subjects and in 72% (60/83) of placebo subjects, consistent with the VA medical center setting for the study. Physical or sexual assault was the second most common traumatic event, and occurred in 16% (14/86) of sertraline subjects and 14% (12/83) of placebo subjects. This was the most common traumatic event among women, occurring in 67% (12/18) of sertraline subjects and 63% (10/16) of placebo subjects. For men, the most common traumatic event was being in war or combat, with 85% (58/68) of sertraline-treated and 88% (59/67) of placebo-treated subjects experiencing this type of trauma.

Men and women differed at baseline on a number of variables. Men were significantly older ($t = -5.3$, $df = 167$, $p < .001$), had longer durations of illness ($t = -4.5$, $df = 167$, $p < .001$), had longer times since the traumatic event ($t = -4.0$, $df = 167$, $p < .0001$), were more often likely to have been exposed to combat-related trauma ($\chi^2 = 79.9$, $df = 1$, $p < .001$), and were more often likely to have a history of substance abuse/dependence ($\chi^2 = 10.2$, $df = 1$, $p < .001$). Men and women, however, had comparable rates of current comorbid major depressive disorder ($\chi^2 = 1.2$, $df = 1$, $p = .26$) and any other current anxiety disorder ($\chi^2 = 0.59$, $df = 1$, $p = .44$).

There were no statistically significant mean differences at baseline between the sertraline and placebo groups on any of the efficacy variables.

Study Treatment

The mean final dose of sertraline was 135 mg/day (SD = 61.9; N = 86). For placebo, the mean final mg equivalent was 172 mg/day (SD = 49.6; N = 83). Among those who completed treatment, the mean daily dose in the sertraline group (weeks 11–12) was 156 mg/day (SD = 49.1; N = 60), and in the placebo group was 181 mg/day (SD = 40.0; N = 69).

Primary Efficacy Measures

At endpoint, the adjusted mean changes on the CAPS-2 total severity score for the sertraline and placebo groups were –13.1 and –15.4, respectively; the difference was not statistically significant. The mixed model analysis also revealed no significant differences in rate of change on the CAPS-2 between sertraline and placebo over the course of the 12-week treatment period ($F = 1.28$, $df = 1,137$; $p = .26$). There were also no significant group differences on the CAPS-2 subscales (reexperiencing/intrusion, avoidance/numbing, hyperarousal) at any visit, including the week 12 visit (completer sample).

At endpoint, the adjusted mean changes for the IES total score were –8.7 and –8.1 for the sertraline and placebo groups, respectively (Table 2). This difference was not significant. There was no significant between-group difference in rate of change for the IES total score over the course of treatment ($F = 1.20$, $df = 1,136$; $p = .28$). For the CGI-S scale, there were no statistically significant

Table 2. Mean Baseline (SD) and Adjusted Change (SE) at Endpoint on Primary and Secondary Efficacy Variables for Posttraumatic Stress Disorder (PTSD) Patients

Measure	Baseline	Change at Endpoint[a]
CAPS-2		
Sertraline	72.1 (19.1)	–13.1 (3.0)
Placebo	73.8 (19.8)	–15.4 (3.1)
IES-total		
Sertraline	40.7 (15.8)	–8.7 (1.8)
Placebo	43.4 (15.6)	–8.1 (1.9)
CGI-S		
Sertraline	4.5 (0.9)	–0.5 (0.1)
Placebo	4.7 (1.0)	–0.6 (0.1)
CGI-I		
Sertraline	…	3.0 (0.2)
Placebo	…	3.0 (0.2)
DTS		
Sertraline	77.2 (27.5)	–11.4 (3.5)
Placebo	80.4 (27.1)	–10.5 (3.5)
HAM-A		
Sertraline	19.3 (7.9)	–4.1 (1.0)
Placebo	20.9 (8.7)	–6.1 (1.1)
HAM-D		
Sertraline	19.7 (8.3)	–2.7 (1.1)
Placebo	20.5 (8.5)	–4.2 (1.1)
PSQI		
Sertraline	12.4 (3.6)	–0.9 (0.4)
Placebo	12.1 (3.4)	–1.6 (0.4)
DES		
Sertraline	51.0 (22.1)	–11.4 (2.8)
Placebo	53.5 (22.0)	–14.5 (2.8)
MISS		
Sertraline	115.8 (15.7)	–4.3 (1.7)
Placebo	118.1 (16.6)	–2.8 (1.7)

[a]Change scores adjusted for baseline, site, and treatment-by-site interaction.
Abbreviations: CAPS-2 = Clinician-Administered PTSD Scale, Part 2; CGI-I = Clinical Global Impressions-Improvement Scale; CGI-S = Clinical Global Impressions-Severity of Illness Scale; DES = Disorders of Extreme Stress–Not Otherwise Specified Scale; DTS = Davidson Trauma Scale; HAM-A = Hamilton Rating Scale for Anxiety; HAM-D = Hamilton Rating Scale for Depression; IES = Impact of Event Scale; MISS = Mississippi Rating Scale for Combat-Related PTSD–Civilian Trauma Version; PSQI = Pittsburgh Sleep Quality Index.
Symbol: … = not applicable.

differences between treatment groups in changes from baseline to endpoint. The mean changes from baseline at endpoint were –0.5 and –0.6 for sertraline and placebo subjects, respectively (Table 2). For the CGI-I, there was also no statistically significant difference between treatment groups at endpoint (mean score of 3.0 for both the sertraline and placebo groups). There was also no statistically significant difference ($F = 0.69$, $df = 1,132$; $p = .41$) on rate of change in the CGI-I over the course of treatment. No significant differences in rate of change on the CGI-S ($F = 0.16$, $df = 1,135$; $p = .69$) were evident.

Responder Rates

There was no significant difference between treatment groups in the proportion of patients meeting responder criteria on the CAPS-2 (30% or greater decrease). For sertraline, 34.5% (29/84) of patients met this definition of clinical response compared with 42.7% (35/82) of placebo patients (Cochran-Mantel-Haenszel $\chi^2 = 1.2$, $df = 1$, $p = .27$). Responder rates as defined on the CGI-I (score of 1 or 2) also were not significantly different (Cochran-Mantel-Haenszel $\chi^2 = 0.25$, $df = 1$, $p = .62$) (sertraline: 36.9% [31/84]; placebo: 41.5% [34/82]).

Table 3. Treatment-Emergent Adverse Events Reported at a Rate ≥ 10%

Adverse Event	Sertraline (N = 86), N (%)	Placebo (N = 83), N (%)
Diarrhea	27 (31.4)	15 (18.1)
Headache	23 (26.7)	20 (24.1)
Insomnia	12 (14.0)	8 (9.6)
Somnolence	12 (14.0)	7 (8.4)
Nausea	18 (20.9)	8 (9.6)
Fatigue	9 (10.5)	1 (1.2)*

*$p < .05$, Fisher exact test for difference between treatment groups.

Secondary Efficacy Assessments

There were no significant differences between treatment groups at endpoint or at any specific study visit on the Davidson Trauma Scale, although the sertraline group evidenced numerically greater improvement at all visits from week 2 to the end of the study. There were also no significant differences between treatment groups at endpoint on the Disorders of Extreme Stress–Not Otherwise Specified scale, the Mississippi Rating Scale for Combat-Related PTSD–Civilian Trauma Version, the HAM-A scale, the HAM-D scale, and the Pittsburgh Sleep Quality Index (Table 2).

Treatment Discontinuation and Adverse Events

The discontinuation rates for the sertraline and placebo groups were 30% (26/86) and 17% (14/83), respectively ($\chi^2 = 4.2$, $df = 1$, $p = .041$). The most frequent reason for discontinuation in the sertraline group was adverse event (13% [11/86] of sertraline subjects vs. 6% [5/83] of placebo subjects; $\chi^2 = 2.3$, $df = 1$, $p = .133$), while in the placebo group, the most common reason for discontinuation was withdrawal of consent (7% [6/83] of placebo subjects vs. 7% [6/86] of sertraline subjects).

In the sertraline group, 86% (74/86) of subjects reported treatment-emergent adverse events in comparison with 72% (60/83) in the placebo group ($\chi^2 = 4.9$, $df = 1$, $p = .027$). The predominant (≥ 10% incidence) treatment-emergent adverse events are given in Table 3. The only adverse event that occurred significantly more frequently in sertraline-treated patients was fatigue (Fisher exact test, $p = .018$). Rates of clinically significant laboratory, vital sign, and electrocardiogram abnormalities were low and not significantly different between the treatment groups.

Moderator Variables

Results indicated that, across treatment groups, neither gender, duration of illness, nor history of alcohol/

substance abuse were related to treatment outcome (CAPS-2, IES, CGI-S, or CGI-I). However, there was a significant main effect for type of trauma on the CAPS-2, and significant interactions of treatment group with gender (on the IES), history of alcohol/substance abuse (on the CGI-S), and type of trauma (on the IES). In addition, there were significant main effects for severity of illness (on the IES, CGI-S, and CGI-I), but no significant severity of illness by treatment interactions. These effects are described below.

The significant main effects for severity of illness as a predictor of change on the IES ($F = 5.8$, $df = 1,144$; $p = .017$), CGI-S ($F = 17.7$, $df = 1,144$; $p = .0001$), and CGI-I ($F = 11.9$, $df = 1,145$; $p = .0007$) were a function of patients with more severe illness showing greater change from baseline to endpoint with sertraline compared with placebo. The significant main effect for type of trauma with the CAPS-2 total score ($F = 4.4$, $df = 1,141$; $p = .039$) was a result of greater improvements found with noncombat traumas (adjusted mean change to endpoint = –22.2, SE = 4.4, N = 48) compared with combat traumas (mean change = –11.7, SE = 2.4, N = 118) across drug and placebo groups. On the IES, the significant ($F = 7.3$, $df = 1,143$; $p = .0077$) type of trauma by treatment interaction was a function of an extremely large placebo response among the small group of patients with noncombat trauma (adjusted mean change = –18.7, SE = 3.7, N = 23) compared with those with combat trauma who received placebo (adjusted mean change = –4.4, SE = 2.1, N = 59), but little difference between those with civilian trauma receiving sertraline (adjusted mean change = –7.1, SE = 3.7, N = 25) compared with those with combat trauma receiving sertraline (adjusted mean change = –9.2, SE = 2.0, N = 59).

The significant ($F = 5.0$, $df = 1,143$; $p = .027$) treatment by gender interaction on the IES was largely due to a large placebo response for women (adjusted mean change = –16.5, SE = 4.6, N = 16) compared with men (adjusted mean change = –6.5, SE = 2.0, N = 66), and a slightly better response to sertraline among men (adjusted mean change = –9.6, SE = 2.0, N = 66) compared with women (adjusted mean change = –4.2, SE = 4.3, N = 18), although pairwise comparisons among these adjusted means yielded no significant differences. Finally, on the CGI-S, the significant treatment by history of alcohol/substance abuse interaction ($F = 4.4$, $df = 1,143$; $p = .039$) was a function of patients on placebo with a history of alcohol/substance abuse responding better than those without a history of alcohol/substance abuse (adjusted mean changes of –0.79 [SE = 0.18] vs. –0.34 [SE = 0.21]), while patients receiving sertraline who had a history of alcohol/substance abuse evidenced poorer outcomes than those who had no history of alcohol/substance abuse (adjusted mean changes of –0.31 [SE = 0.18] vs. –0.67 [SE = 0.21]). These differences, however, were not significant when pairwise comparisons were performed.

DISCUSSION

The current study did not find sertraline to be efficacious at endpoint within a sample of VA patients with PTSD. The lack of efficacy found for sertraline in this VA setting stands in contrast to 2 previous placebo-controlled studies that demonstrated clear evidence for the efficacy of sertraline as a treatment of civilian PTSD,[12,13] and 1 small placebo-controlled study of combat-related PTSD conducted in Israel that showed some evidence for the efficacy of sertraline.[53] There were, however, several differences between the present study and the one conducted in Israel. The sample for the study conducted in Israel had a shorter duration of PTSD symptoms and higher initial CAPS-2 scores (mean of 94 vs. 73 in the current study).

We explored the role of a number of potential predictor/moderator variables in relation to efficacy. For both placebo and sertraline groups, combat-related PTSD was associated with relatively poorer outcomes on the CAPS-2 than non–combat-related PTSD in veterans treated in VA clinics. Moreover, the overall amount of improvement from baseline to endpoint in the current study was substantially less than that found in previous studies of non–combat-related PTSD. For example, on the IES, mean change to endpoint in the current study was –8.7 and –8.1 for sertraline and placebo, respectively, while a previous study[12] reported changes of –16.2 for sertraline and –12.1 for placebo. Similarly, changes on the CAPS-2 were –13.1 and –15.4 in the current study, and –33.0 and –23.2 in the Brady et al.[12] study, for sertraline and placebo, respectively.

One interpretation of these findings would suggest that sertraline, or SSRIs, are only effective for PTSD patients with civilian trauma. Such a conclusion is not warranted for the following reasons: First, sertraline was effective with Israeli veterans with PTSD, with combat exposure related to a more positive response from sertraline.[53] Second, a large multisite randomized trial conducted after the present study found that, among the subgroup of participants with combat-related trauma related to recent UN or NATO conflicts, fluoxetine was significantly superior to placebo.[19] Third, although within the current study sertraline-treated patients with noncombat PTSD improved more than those with combat PTSD on the CAPS-2, patients with noncombat PTSD actually had slightly worse outcomes than those with combat-related PTSD on the IES. Furthermore, there was no significant main effect for type of trauma on the CGI-I, or CGI-S. Finally, it has been argued elsewhere[41] that Vietnam veterans receiving treatment for PTSD within VA settings decades after their combat trauma are not representative of military veterans with combat-related PTSD but, rather, may repre-

sent the most severely impaired, chronic, and treatment-refractory cohorts. Negative findings from a recent large-scale multisite randomized trial of psychosocial group treatments for PTSD among Vietnam veterans within the VA health care system are consistent with the negative results from the present study, and probably for the same reasons.[54]

Examination of other potential factors influencing efficacy outcomes revealed no consistent evidence for gender, duration of illness, and history of alcohol/drug abuse as main effect predictors (across treatment groups) or in interaction with group (differential response to sertraline vs. placebo). No difference in sertraline response rates between men and women in pooled data from 2 placebo-controlled trials in civilian PTSD has been reported.[55] Similarly, paroxetine has been reported to be equally efficacious for men and women with chronic civilian PTSD.[14] On the basis of data from the current study, taken together with the results of previous studies, it is unlikely that gender is a major factor contributing to lack of sertraline efficacy in a VA population. As would be expected, greater severity of illness was associated with a greater change from baseline to endpoint for patients treated with both drug and placebo (patients who are more severe at baseline have more room for improvement on the efficacy measures). However, no differential response to sertraline versus placebo was found depending on initial illness severity.

No previous studies of SSRIs for PTSD have systematically examined duration of illness or history of alcohol/drug abuse as moderators of treatment response. The lack of previous findings and reduced statistical power for detecting interaction effects in the current study make it difficult to definitively rule out these factors in understanding the lack of sertraline efficacy in the VA setting. It should be noted that the duration of illness in previous sertraline civilian PTSD studies[12,13] was 12 to 13 years, suggesting that sertraline can be efficacious for patients with chronic civilian PTSD. In regard to alcohol/drug abuse, some research indicates that the relation of current alcohol or drug use to sertraline efficacy may be complex. Among patients with civilian PTSD and comorbid alcohol dependence, those with less severe alcohol dependence and early-onset PTSD had a better response to sertraline compared with placebo, but placebo actually was superior to sertraline among those with more severe alcohol dependence and later onset PTSD.[56] Thus, it may be important to examine subtypes of alcohol- or drug-dependent individuals in regard to sertraline efficacy, and current versus previous history may be relevant.

Another factor that has been suggested as contributing to the lack of efficacy of sertraline and other medications as treatments for PTSD in VA settings is the fact that many VA patients receive financial compensation for their illness. However, outpatients with PTSD in VA treatment settings who were seeking compensation have been found to actually have better outcomes than those not receiving compensation.[57] The current study was not able to assess this question because it did not collect information on disability applications or payments or other financial compensation available to VA patients.

Sertraline was found to be well tolerated in this sample. Only 1 adverse event (fatigue) occurring at a rate greater than 10% was significantly more prevalent in the sertraline group compared with the placebo group. In addition, there was not a significantly higher rate of discontinuation due to adverse events for sertraline-treated patients (13%) compared with placebo-treated patients (6%). However, overall the rate of discontinuation for sertraline (30%) was higher than for placebo (17%). The factors responsible for the larger discontinuation rate are not clear but might suggest underreporting of adverse events.

Limitations of the current study include the fact that the study was not designed as an a priori test (with high statistical power) for examining potential moderator variables, and no assessment of disability payments was made. In addition, larger sample sizes would be needed to unravel the potential interrelations and interactions among the variables examined here (gender, type of trauma, duration of illness, and history of alcohol/substance abuse), and more detailed patient histories with respect to previous traumas and medical histories would be helpful. Thus, further research is needed to confirm the role of these variables in relation to the efficacy of sertraline for PTSD.

In conclusion, the current study failed to find evidence for the efficacy of sertraline treatment of PTSD in a VA setting despite its proven efficacy in the civilian population. The lack of efficacy did not appear to be due to the influence of gender, type of trauma, duration of illness, or history of alcohol/drug abuse. Further research is needed to address the patient, illness, and setting variables that might be contributing to the presence or lack of efficacy of sertraline and other medications in the treatment of PTSD.

Drug names: citalopram (Celexa and others), cycloserine (Seromycin), fluoxetine (Prozac and others), mirtazapine (Remeron and others), paroxetine (Paxil and others), phenelzine (Nardil), prazosin (Minizide, Minipress, and others), risperidone (Risperdal), sertraline (Zoloft and others), venlafaxine (Effexor and others).

Acknowledgments: We would like to acknowledge the editorial assistance of Paul Crits-Christoph, Ph.D., in the preparation of the draft manuscript, and Tom Metzler, who provided statistical assistance. Dr. Crits-Christoph has received consulting income from Pfizer, Bristol-Myers Squibb, Cephalon, and Alkermes, and Mr. Metzler has nothing to disclose. We would like to express our appreciation to the investigators who participated: Neal Kline, M.D.; Mark H. Rapaport, M.D.; June Corwin, Ph.D.; Israel Liberzon, M.D.; Joseph Westermeyer, M.D., Ph.D., M.P.H.; Jonathan Davidson, M.D.; Michael Hertzberg, M.D.; Bruce Kagan, M.D.; Bruce Perry, M.D., Ph.D.; Mark B. Hamner, M.D.; and Thomas A. Mellman, M.D.

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