Efficacy and Safety of Sertraline Treatment of Posttraumatic Stress isorder

A Randomized Controlled Trial

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Context espite the high prevalence, chronicity, and associated comorbidity of posttraumatic stress disorder (PTS) in the community, few placebo-controlled studies have evaluated the efficacy of pharmacotherapy for this disorder.

Objective To determine if treatment with sertraline hydrochloride effectively diminishes symptoms of PTS of moderate to marked severity.

esign Twelve-week, double-blind, placebo-controlled trial preceded by a 2-week, single-blind placebo lead-in period, conducted between May 1996 and June 1997.

Setting Outpatient psychiatric clinics in 8 academic medical centers and 6 clinical research centers.

Patients A total of 187 outpatients with a *iagnostic and Statistical Manual of Mental isorders, Revised Third Edition* diagnosis of PTS and a Clinician Administered PTS Scale Part 2 (CAPS-2) minimum total severity score of at least 50 at baseline (mean age, 40 years; mean duration of illness, 12 years; 73% were women; and 61.5% experienced physical or sexual assault).

Intervention Patients were randomized to acute treatment with sertraline hydrochloride in flexible daily dosages of 50 to 200 mg/d, following 1 week at 25 mg/d (n=94); or placebo (n=93).

Main Outcome Measures Baseline-to-end-point changes in CAPS-2 total severity score, Impact of Event Scale total score (IES), and Clinical Global Impression–Severity (CGI-S), and CGI-Improvement (CGI-I) ratings, compared by treatment vs placebo groups.

Results Sertraline treatment yielded significantly greater improvement than placebo on 3 of the 4 primary outcome measures (mean change from baseline to end point for CAPS-2 total score, –33.0 vs –23.2 [*P*=.02], and for CGI-S, –1.2 vs –0.8 [*P*=.01]; mean CGI-I score at end point, 2.5 vs 3.0 [*P*=.02]), with the fourth measure, the IES total score, showing a trend toward significance (mean change from baseline to end point, –16.2 vs –12.1; *P*=.07). Using a conservative last-observation-carried-forward analysis, treatment with sertraline resulted in a responder rate of 53% at study end point compared with 32% for placebo (*P*=.008, with responder defined as >30% reduction from baseline in CAPS-2 total severity score and a CGI-I score of 1 [very much improved], or 2 [much improved]). Significant (*P* .05) efficacy was evident for sertraline from week 2 on the CAPS-2 total severity score. Sertraline had significant efficacy vs placebo on the CAPS-2 PTS symptom clusters of avoidance/numbing (*P*=.02) and increased arousal (*P*=.03) but not on reexperiencing/intrusion (*P*=.14). Sertraline was well tolerated, with insomnia the only adverse effect reported significantly more often than placebo (16.0% vs 4.3%; *P*=.01).

Conclusions Our data suggest that sertraline is a safe, well-tolerated, and effective treatment for PTS .

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increased arousal (startle reactions, poor concentration, irritability and jumpiness, insomnia, or hypervigilance). With a minimum symptom duration of 1 month at a level of severity necessary to impair an individual's functioning, PTSD has been estimated to have a lifetime prevalence in the range of 5% to 12%, based on epidemiological surveys,[1,4,5] with women having twice the prevalence rate of men.

Fre uently, PTSD is a chronic illness, with a median time to recovery in the range of 3 to 5 years.[1,6] The disorder is associated with unusually high rates of lifetime psychiatric comorbidity,[1,5,7] especially major depression (odds ratio relative to non-PTSD sample, approximately 4-7), alcoholism and drug abuse (odds ratio, approximately 3), and panic disorder (odds ratio in the range of 3-20). Research has shown that previous psychiatric history is a risk factor for development of PTSD following trauma exposure.[1,8-10] Furthermore, patients with PTSD often have subse uent onset of another psychiatric disorder. Analysis of epidemiological data relating to age at time of trauma and onset of PTSD diagnosis suggests that when PTSD occurs in conjunction with a mood or anxiety illness, it constitutes the primary disorder in 41% to 58% of women and 29% to 51% of men.[1] The high chronicity, severity, and comorbidity of PTSD are associated with high levels of functional and psychosocial disability,[11,12] as well as increased somatic complaints and health care use.[13-16]

An empirical review published in 1992[17] identified only 5 controlled trials of medication treatment,[18-22] all of which were limited to men (mostly combat veterans). This review found "modest efficacy" for pharmacological and behavioral treatments with "the strongest efficacy favoring behavioral techni ues." Only 3 double-blind, placebo-controlled studies have been published since that review. Two reported conflicting results for the never-marketed monoamine oxidase type A inhibitor brofaromine.[23,24] A third study reported positive results for fluoxetine (n=10) compared with placebo (n=13) in a subgroup of civilian patients with PTSD,[25] while no significant differences between fluoxetine and placebo were found in a subgroup of patients with combat-related PTSD treated in a Veterans Affairs clinic setting.

The selective serotonin reuptake inhibitor antidepressants appear promising in the treatment of PTSD for various reasons. Optimally, a candidate therapy should be well-tolerated and able to effectively treat the core clinical features of PTSD and common affective and anxiety disorder comorbidity, as well as to improve psychosocial functioning. Sertraline, one of the most widely prescribed selective serotonin reuptake inhibitor antidepressants, effectively attenuates the behavioral syndrome that occurs in animals after exposure to uncontrollable stress,[26] which has been interpreted as an animal model of PTSD.[27,28] Two small, open-label studies[29,30] have shown efficacy for sertraline, 1 in the treatment of those with PTSD due to sexual assault and 1 in patients with comorbid alcoholism and PTSD. The efficacy of sertraline in treating depression,[31-33] panic disorder,[34-36] and obsessive-compulsive disorder[37,38] are well established. In light of this clinical activity, we conducted a large, placebo-controlled study from May 1996 to June 1997 to examine the efficacy of sertraline in the treatment of PTSD. Because of the marked impairment in occupational, health, and psychosocial functioning associated with PTSD, uality-of-life, psychosocial, and symptomatic outcomes were assessed.[7,12]

METHO S

Patient Sample

The subjects were male and female outpatients aged 18 years and older who met *iagnostic and Statistical Manual of Mental isorders, Revised Third Edition* (*SM-III-R*) criteria for a principal diagnosis of PTSD as determined by part 1 of the Clinician Administered PTSD Scale.[39,40] A minimum 6-month duration of PTSD illness was re uired (exceeding the 1-month minimum re uired by *SM-III-R*), as well as a total severity score of at least 50 (range, 0-136) on the Clinician Administered PTSD Scale, Part 2 (CAPS-2) at the end of a 2-week placebo run-in period; subjects were at least moderately ill. All patients were re uired to be free of psychotropic medication for at least 2 weeks prior to beginning treatment. Women's participation was contingent on negative results of a beta–human chorionic gonadotropin pregnancy test and stable use of a medically accepted form of contraception. Exclusion criteria were: (1) current or past history of bipolar, schizophrenic, or other psychotic disorder; (2) current organic mental disorder, factitious disorder or malingering, or *primary* diagnosis of major depression, obsessive-compulsive disorder, or other anxiety disorders; (3) alcohol or substance dependence or abuse in the past 6 months; (4) evidence of clinically significant hepatic or renal disease or any other acute or unstable medical condition that might interfere with the safe conduct of the study; (5) intolerance or hypersensitivity to sertraline or nonresponse to a previous ade uate trial; (6) current use of any medication (except chloral hydrate, taken as needed) with clinically significant psychotropic activity within 2 weeks of randomization (or 5 weeks for fluoxetine); (7) any cognitive-behavioral therapy during the trial; and (8) psychotherapy that was initiated or that ended during the trial.

The research was conducted at outpatient psychiatric clinics in 8 academic medical centers and 6 clinical research centers. The study was approved by the institutional review board at each of the 14 collaborating centers or by a national institutional review board. The benefits and risks of study participation were fully explained to each patient, and written informed consent was obtained.

Study esign

Following a 2-week, single-blind placebo run-in period, patients were randomized to 12 weeks of double-blind parallel treatment with either sertraline or matched placebo. To be randomized, patients had to demonstrate at baseline a minimum level of PTSD symptom severity as indi-

cated by a CAPS-2 severity score of at least 50. There were no other operationally defined placebo responder exclusion criteria. Treatment was initiated at 25 mg/d for 1 week, with flexible daily dosing and 50 to 200 mg/d thereafter, based on clinical response and tolerability. Dosing changes were made in 50-mg increments at no less than weekly intervals unless required for safety. At the conclusion of 12 weeks of double-blind treatment, patients were eligible to enroll in a 24-week open-label sertraline treatment protocol. Entry into the open-label study was not dependent on responder status, nor was the blinding for the acute phase broken at the time of entry into open-label treatment.

Assessments

Patients were evaluated for study entry by a semistructured psychiatric interview and administration of Part 1 of the structured Clinician Administered PTSD Scale,[39,40] an instrument rating lifetime history and current symptoms of PTSD as defined in *SM-III-R*. A medical history was taken and a physical examination and routine laboratory testing were performed. Severity of PTSD symptoms at baseline was rated by the investigators using CAPS-2 and the Clinical Global Impression–Severity scale (CGI-S).

Efficacy and Safety

The primary outcome measures for the study consisted of the 17-item total severity score of the CAPS-2[39,40] (a 30-item investigator-completed scale that rates the frequency and intensity of PTSD symptoms on separate 5-point scales); the Impact of Event Scale (IES)[41,42] (a 15-item patient-completed scale that rates intrusion and avoidance symptoms on a 6-point severity scale); and the investigator-rated CGI-S and Clinical Global Impression–Improvement scale (CGI-I).[43] Primary outcome assessments were performed at baseline and at study treatment weeks 1, 2, 3, 4, 6, 8, 10, and 12 (or at the time of discontinuation if prior to week 12). The CAPS-2 was not administered at weeks 1 and 3, and the CGI-I was not administered at baseline.

The secondary outcome measures consisted of (1) the 17-item Davidson Trauma Scale (DTS)[44,45] that allows patients to rate the 17 *SM-III-R*–defined PTSD symptoms on a 5-point frequency and a 5-point severity scale; (2) the investigator-rated 24-item Hamilton Depression Rating scale[46]; (3) a validated short form of the patient-rated Quality of Life Enjoyment and Satisfaction scale[47]; (4) subscales of the CAPS-2, IES, and DTS that rate the severity of PTSD symptom clusters (re-experiencing/intrusion, avoidance/numbing, and increased arousal); and (5) subscales of the CAPS-2 that measure associated features and functional impairment. Secondary outcome assessments were performed at baseline and at the end of study treatment weeks 2, 4, 6, 8, 10, and 12 (except DTS, which was also completed at the end of weeks 1 and 3; and the Hamilton Depression Rating scale and Quality of Life Enjoyment and Satisfaction scale, which were completed only at baseline and week 12).

Safety assessments included evaluation at each study visit of weight, sitting blood pressure, and heart rate. Adverse effects that were spontaneously reported or observed were recorded with regard to their time of onset, duration, severity, action taken, and outcome. Use of concomitant medications was recorded in terms of daily dosage, stop and start dates, and reason for use. Laboratory assessments (eg, clinical chemistry, hematology, and urinalysis) were performed at initial screening and repeated at weeks 6 and 12 (or at the time of study discontinuation). A physical examination and electrocardiogram were performed at baseline and at week 12 or discontinuation. Compliance was monitored by counts of returned medication, and patients were counseled if they were found to be noncompliant.

Statistical Methods

Baseline characteristics were compared between treatment groups using analysis of variance or χ^2 tests (for sex). Main efficacy analyses were performed using change from baseline to end point during the 12-week treatment period. Efficacy variables were analyzed via analysis of covariance, using the effects of site and treatment in the model and baseline scores as the covariates. For the CGI-I scale, there is no baseline value; therefore, an analysis of variance was performed on the end point score with site and treatment in the model. Treatment by site interactions were examined in all analyses, but none were significant and interaction terms were deleted from the analysis. All statistical tests were 2-sided and performed at the .05 level of significance.

Clinical response to treatment was defined as a 30% or greater decrease in CAPS-2 scores and a CGI-I rating of 1 (very much improved) or 2 (much improved). Analysis of responder rates used a Mantel-Haenszel χ^2 statistic stratified by site.

The incidence of adverse events, the proportion of patients who discontinued treatment because of adverse events, and the incidence of clinically significant laboratory abnormalities were compared between treatment groups using the Fisher exact test. Changes in vital signs (blood pressure, heart rate, body weight) were compared for the treatment groups using the Wilcoxon rank sum test.

Finally, the temporal course of response to treatment was examined using a mixed-effects model for longitudinal data. For the CAPS-2 total severity score, IES, and DTS, the change from baseline to each treatment week was fit to linear and quadratic terms of duration of treatment. The CGI-I score at each treatment visit was fit directly to linear and quadratic terms of duration of treatment. We examined the response curves for each treatment group and compared the difference.

RESULTS

Demographic and Clinical Characteristics

A total of 187 patients were randomly assigned to sertraline (n=94) or placebo (n=93), of whom 93 (99%) sertraline-treated patients and 90 (97%) placebo-treated patients were available for at least 1 postrandomization efficacy assessment. Efficacy analyses

were performed on the latter group, omitting the 1 patient taking sertraline and the 3 patients taking placebo who were unavailable for postrandomization assessment.

For the total randomized sample there were no significant differences between the treatment groups in any of the baseline demographic and clinical characteristics (TABLE 1). Women constituted the majority of the sample. Ages ranged from 18 to 69 years, with 65% of the sample being younger than 45 years. An analysis by sex revealed no significant differences in any of the baseline variables. There were no significant differences between the treatment groups in the types of trauma experienced (TABLE 2). Thirty-eight percent of patients in the sertraline group and 42% of patients in the placebo group reported having received treatment in the previous 5 years for symptoms of PTSD, depression, anxiety, or sleep disturbance, although most had not received a formal diagnosis of PTSD. Of those patients who received symptomatic treatment, 80% in the sertraline group and 68% in the placebo group reported a good response to prior symptomatic treatment ($\chi^2_1 = 2.52$, $P = .11$).

FIGURE 1 shows patient numbers and disposition through the course of treatment.

Treatment and Tolerability

The mean (SD) daily dosage of sertraline at study end point was 133.3 (59.2) mg, while the dosage for those who completed the study was 151.3 (51.2) mg. Sertraline was well tolerated overall. The adverse events reported by at least 10% of patients were, for sertraline and placebo, respectively: headache, 20.2% vs 28.3% ($P = .23$); diarrhea, 23.4% vs 19.6% ($P = .59$); malaise, 17.0% vs 15.2% ($P = .84$); nausea, 16.0% vs 12.0% ($P = .53$); insomnia, 16.0% vs 4.3% ($P = .01$); drowsiness, 12.8% vs 9.8% ($P = .64$); and dry mouth, 11.7% vs 4.3% ($P = .10$).

Twenty-nine patients discontinued sertraline treatment (30.9%) compared with 25 patients discontinuing placebo treatment (27.2%, $P = .63$). The primary reasons cited for discontinuation in the sertraline and placebo groups, respectively, were: insufficient therapeutic response (3.2% vs 2.2%; $P > .99$); adverse events (5.3% vs 5.4%; $P > .99$); laboratory abnormality (3.2% vs 0%; $P = .25$); protocol violation (1.1% vs 0%; $P > .99$); lost to follow-up (10.6% vs 2.2%; $P = .03$); did not meet entrance criteria (1.1% vs 0%; $P > .99$); withdrawal of consent (4.3% vs 14.4%; $P = .02$); and miscellaneous other reasons (2.1% vs 3.3%; $P = .68$).

Table 1. emographic and Clinical ata

Variable	Sertraline (n = 94)	Placebo (n = 93)	Value
Sex, %			
Female	75.5	71.0	.48
Male	24.5	29.0	
Age, mean (S), y	40.2 (9.6)	39.5 (10.6)	.54
Race, %			
Black	14.9	8.6	.26
White	80.9	88.2	
Other	4.3	3.2	
Marital status, %			
Currently married or living with partner	44	41	.91
Never married	29	29	
ivorced or separated	25	28	
Widowed	2	2	
uration of illness, mean (S), y	13.1 (11.8)	11.2 (12.7)	.30
Time from traumatic event, mean (S), y	19.9 (13.5)	17.4 (15.5)	.28
Current major depression, %	36	30	.38
Current anxiety disorder, %	18	14	.44
History of alcohol dependence/abuse, %	22	30	.23
History of substance dependence/abuse, %	14	14	>.99

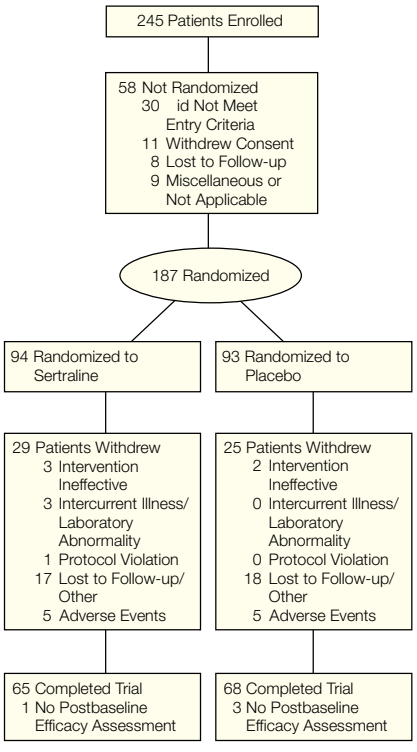
Percentages may not add to 100% due to rounding.

Table 2. Frequency of Trauma by Category

Type of Trauma	No. (%) of Patients: Sertraline (n = 94)	No. (%) of Patients: Placebo (n = 93)	Value
Serious unintentional injury or fire	5 (5.3)	11 (11.8)	.13
Physical or sexual assault	56 (59.6)	59 (63.4)	.65
Seeing someone hurt or die	10 (10.6)	6 (6.5)	.43
Being in war or combat	7 (7.4)	4 (4.3)	.54
Natural disaster	0 (0.0)	1 (1.1)	.50
Miscellaneous other events	16 (17.0)	12 (12.9)	.54

Such as kidnapping.

Figure 1. Flow iagram for the Study



Treatment-emergent laboratory abnormalities led to study discontinuation in 2 patients receiving sertraline treatment: 1 patient at day 51 because of decreases in hemoglobin from 92 to 81 g/L, a second patient at day 44 when an increase was noted in alanine aminotransferase from 11 to 150 U/L and in aspartate aminotransferase from 15 to 50 U/L. There were no statistically significant differences between patients treated with sertraline vs placebo in vital signs or electrocardiographic results. Mean change in body weight during study treatment for sertraline and placebo, respectively, was –1.3 kg vs –0.3 kg (P=.01). One sertraline and 1 placebo patient had serious adverse events, but neither event was considered treatment-related.

Treatment Efficacy

Treatment with sertraline yielded statistically significantly greater efficacy than placebo at study end point (based on a last-observation-carried-forward analysis) on 3 of the 4 a priori primary outcome measures (TABLE 3). The difference between the mean CAPS-2 change scores at end point was 9.8 (95% confidence interval, 1.8-17.7; P=.02); the difference between the mean CGI-S change scores at end point was 0.5 (95% confidence interval, 0.1-0.8; P=.01); the difference between the mean CGI-I scores at end point was 0.4 (95% confidence interval, 0.1-0.8; P=.02). Improvement in the IES total score showed only a trend toward significance (P=.07), with a difference between the mean IES change scores at end point e ual to 4.1 (95% confidence interval, –0.4 to 8.7). Patients taking sertraline also showed significantly greater improvement than placebo on all secondary measures (Table 3, TABLE 4, and TABLE 5). Patient ratings confirmed clinician assessments, with a significant advantage (P=.003) found for sertraline compared with placebo on the DTS.

Global improvement in primary and secondary outcome measures was reflected in the significantly greater improvement observed for sertraline treatment at study end point on both the CGI-S (P=.01) and the CGI-I scores (P=.02). Using the conservative last-observation-carried-forward analysis, treatment with sertraline resulted in a responder rate of 53% at study end point compared with 32% for placebo (P=.008 with responder defined as >30% reduction from baseline in CAPS-2 total severity score and a CGI-I score of 1 [very much improved] or 2 [much improved]).

FIGURE 2 shows a significantly steeper improvement slope with sertraline compared with placebo on both CAPS-2 and IES measures. Additional random regression analyses also found steeper improvement slopes in favor of sertraline for the DTS (t_{1206}= –4.58; P .001) and for the CGI-I score (t_{1052}= –2.71; P .001). The benefit of sertraline treatment was evident relatively early, with a 25% reduction in the mean CAPS-2 total severity score by week 2. A statistically significant advantage over placebo was maintained from week 2. The time course of improvement was similar for the IES, although the degree of statistical significance was less in comparison with the significance for the CAPS-2 scale.

Improvement in PTS Symptom Clusters

Table 4 provides a summary of the effect of the 2 study interventions on the 3 core PTSD symptom clusters. The magnitude of the treatment effect (reduction in mean symptom cluster score as a percentage of baseline score) for sertraline was similar for all 3 symptom clusters (40%-50%).

Effect of Study Treatment on Functional and Quality-of-Life Measures

Among those who completed the study, sertraline treatment was associated not simply with an improvement in PTSD symptom scores but in a significant improvement in measures of social and occupational functioning, as well as perception of improved uality of life (Table 5). A last-observation-carried-forward analysis of the same data found similar results with adjusted mean (SE) change scores for sertraline and placebo, respectively, of –1.2 (0.11) vs –0.7 (0.11) (P=.001) for social functioning,

Table 3. Effect of Study Treatment on Primary and Secondary Efficacy Measures

Efficacy Measures (Adjusted Scores)	Mean Score: Sertraline (n = 93)	Mean Score: Placebo (n = 90)	Value
CAPS-2 total score			
Baseline	76.6 (17.5)	75.1 (17.7)	
Change	–33.0 (2.8)	–23.2 (2.9)	.02
End point	43.4 (28.1)	51.9 (28.7)	
IES total score			
Baseline	37.7 (15.7)	36.7 (15.4)	
Change	–16.2 (1.6)	–12.1 (1.6)	.07
End point	21.0 (17.6)	24.5 (17.5)	
CGI-Severity			
Baseline	4.5 (0.73)	4.6 (0.72)	
Change	–1.2 (0.13)	–0.8 (0.13)	.01
End point	3.3 (1.3)	3.8 (1.2)	
CGI-Improvement	2.5 (0.13)	3.0 (0.14)	.02
HAM- total score			
Baseline	21.5 (6.9)	20.2 (8.0)	
Change	–8.6 (1.3)	–5.0 (1.2)	.04
End point	13.7 (10.4)	15.8 (10.4)	
avidson PTS scale total score			
Baseline	71.9 (24.1)	68.5 (27.8)	
Change	–28.1 (2.8)	–16.1 (2.8)	.003
End point	43.2 (29.9)	52.2 (31.3)	

CAPS-2 indicates Clinician Administered Posttraumatic Stress isorder (PTS) Scale Part 2; IES, Impact of Event Scale; CGI, Clinical Global Impression; and HAM- , Hamilton epression Rating Scale. A decreased CAPS-2 score represents improvement. Baseline and end point scores are mean (S), and change scores are mean (SEM).

Table 4. Effect of Study Treatment on CAPS-2 and IES Symptom Clusters

PTS Symptom Clusters and Associated Features (Adjusted Scores)	Mean Score: Sertraline (n = 93)	Mean Score: Placebo (n = 90)	Value for Change
Reexperiencing/intrusion			
CAPS-2			
Baseline	15.5 (6.2)	15.5 (6.3)	
Change	–6.9 (0.72)	–5.4 (0.73)	.14
End point	8.5 (7.0)	10.0 (7.9)	
IES			
Baseline	17.2 (8.6)	17.3 (9.1)	
Change	–7.1 (0.86)	–5.4 (0.87)	.16
End point	10.0 (9.2)	11.7 (9.5)	
Avoidance/numbing			
CAPS-2			
Baseline	33.6 (8.2)	32.2 (8.8)	
Change	–14.6 (1.31)	–10.0 (1.34)	.02
End point	18.5 (13.4)	22.6 (12.3)	
IES			
Baseline	20.5 (9.9)	19.3 (8.6)	
Change	–9.0 (0.92)	–6.8 (0.93)	.09
End point	11.0 (9.6)	12.8 (9.7)	
Arousal			
CAPS-2			
Baseline	27.5 (7.7)	27.4 (7.8)	
Change	–11.4 (1.05)	–0.8 (1.06)	.03
End point	16.4 (10.2)	19.3 (11.1)	
Associated features			
CAPS-2			
Baseline	25.6 (9.5)	23.8 (9.8)	
Change	–10.8 (1.06)	–7.5 (1.08)	.03
End point	14.3 (11.5)	16.4 (10.2)	

CAPS-2 indicates Clinician Administered Posttraumatic Stress isorder (PTS) Scale Part 2; IES, Impact of Event Scale. Baseline and end point scores are mean (S), and change scores are mean (SEM).

Table 5. Effect of Study Treatment on Functional and Quality-of-Life Measures Among Intent-to-Treat Population (LOCF Analysis)

Functional or Quality-of-Life Measure (Adjusted Scores)†	Mean Score: Sertraline (n = 93)	Mean Score: Placebo (n = 90)	Value for Change
CAPS-2 social functioning			
Baseline	2.7 (0.85)	2.7 (0.78)	
Change	–1.2 (0.11)	–0.7 (0.11)	.001
End point	1.5 (1.1)	2.0 (1.1)	
CAPS-2 occupational functioning			
Baseline	1.8 (0.94)	2.0 (0.95)	
Change	–0.7 (0.10)	–0.4 (0.10)	.02
End point	1.2 (1.0)	1.6 (1.0)	
Q-LES-Q total score			
Baseline	53.8 (11.4)	58.2 (13.3)	
Change	11.7 (2.1)	3.3 (1.9)	.004
End point	65.4 (16.9)	60.5 (16.7)	
Q-LES-Q satisfaction score			
Baseline	2.6 (0.77)	2.8 (0.89)	
Change	0.7 (0.16)	0.2 (0.14)	.05
End point	3.3 (1.2)	3.0 (1.2)	

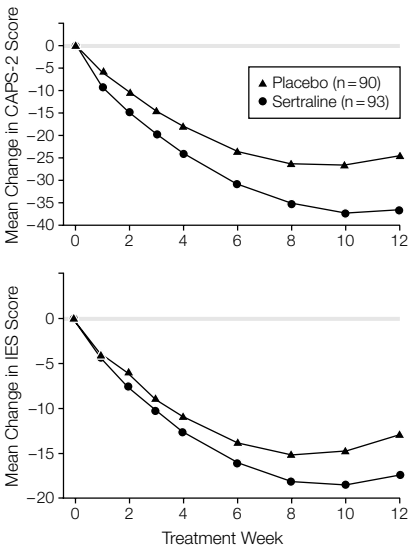
LOCF indicates last observation carried forward; CAPS-2, Clinician Administered Posttraumatic Stress isorder Scale Part 2; and Q-LES-Q, Quality of Life Enjoyment and Satisfaction Questionnaire. Baseline and end point scores are mean (S), and change scores are mean (SEM).
†A decreased CAPS-2 score represents improvement, while an increase in Q-LES-Q score represents improvement.

measured by CAPS-2; –0.7 (0.10) vs –0.4 (0.10) (P=.02) for occupational functioning measured by CAPS-2; and 11.7 (2.1) vs 3.3 (1.9) (P=.004) for Quality of Life Enjoyment and Satisfaction Questionnaire total score.

COMMENT

This multicenter, randomized clinical trial found sertraline to be significantly more effective than placebo in the treatment of PTSD across a spectrum of illness-specific global and functional outcome measures. In the efficacy analysis, 53% of patients were much or very much improved at treatment end point (P=.008 vs placebo), with 70% of the reduction in PTSD symptom severity on the CAPS-2 and IES achieved within the first 4 weeks of treatment (Figure 2). The placebo response rate of 32% was comparable with what has been observed in previous multicenter PTSD clinical trials[23,24] as well as across most acute treatment

Figure 2. Results of Random Regression Analyses Comparing the Effects of Sertraline vs Placebo



Mean change in Clinician Administered PTS Scale Part 2 (CAPS-2) scores from baseline (top) (t_{893}= –3.68; P .001) and the Impact of Event Scale (IES) score from baseline (bottom) (t_{1236}= –3.00; P=.003), estimated from random regression analyses plotted over the 12-week course of study treatment. Gray line indicates baseline. Negative change in scores reflects clinical improvement.

studies of patients diagnosed as having affective or anxiety disorders.

The efficacy of sertraline was significant compared with placebo in reducing symptom severity for the *SM-III-R*–defined PTSD symptom clusters of arousal and avoidance/numbing but not for the third symptom cluster, reexperiencing/intrusion. Nonetheless, the percentage reduction from baseline in symptom severity was the same for this third cluster as for the first 2 clusters (41%-45%; Table 4). The baseline severity scores for the reexperiencing/intrusion cluster were much lower than the baseline scores for the other 2 clusters, making statistical significance harder to demonstrate, especially since the study was not powered to show a significant drug vs placebo difference on PTSD symptom cluster subanalyses.

The benefits of pharmacotherapy in treating PTSD have been shown to be moderate and less effective than cognitive and/or behavioral therapies.[17] Although published studies of cognitive and/or behavioral therapies that are rigorously designed and have sufficient power are still limited in number, available data consistently suggest benefit in certain types of patients with PTSD, particularly women who have experienced sexual assault.

Since the 1992 treatment review,[17] 3 double-blind, placebo-controlled studies have been published that suggest efficacy for monoamine oxidase inhibitor and selective serotonin reuptake inhibitor antidepressants.[23-25] Fluoxetine showed promise in civilians with PTSD[25] but, consistent with previous findings, was not found to have efficacy in combat-related PTSD treated in a Veterans Affairs clinic setting. The magnitude of the treatment effect observed with fluoxetine was similar to that in the current study, but fluoxetine was not well tolerated, with a 41% attrition rate, 81% incidence of diarrhea, and 65% incidence of increased sweating, suggesting the possibility of fluoxetine-induced autonomic effects. In contrast, insomnia was the only adverse event in this trial with a significantly higher incidence in patients taking sertraline vs placebo; the rate of treatment-emergent adrenergic symptoms was also low and not significant compared with placebo.

The short-term results achieved in the current study are particularly impressive, given that the mean duration of PTSD was more than 10 years (Table 1). In 1 large, community survey,[1] the mean duration of illness was reported to be 3 to 5 years, and "one-third of patients never fully remitted even after many years, and irrespective of whether they were in treatment." This degree of chronicity is associated with pervasive adverse effects on psychosocial functioning,[7,12] as well as prominent somatic complaints and high use of health care services.[7,13-15] Despite the chronicity and degree of psychosocial impairment reported by study patients at baseline, the symptomatic improvement achieved by taking sertraline during treatment was rapidly translated into significant improvement in social and occupational functioning and perceived uality of life (Table 5). Whether treatment with sertraline yields a comparable cost offset in terms of reduced health care use awaits the results of future research.

Primary care providers underdiagnose and undertreat patients with PTSD because of the complex clinical presentation and comorbidity common to the illness.[1,48] Comorbidity rates observed in the current study are consistent with this complex clinical presentation, with a 30% to 36% rate of major depression, a 14% to 18% rate of anxiety disorder, a 22% to 30% history of alcohol dependence or abuse, and a 14% history of substance dependence and/or abuse (current alcohol and substance abuse problems were reasons for exclusion). The exclusion from the study of patients with primary affective illness or anxiety disorder diagnoses may have reduced the incidence of comorbid affective illness in the current sample compared with what has been reported in the community.[1] A potential therapeutic advantage of sertraline as a treatment for PTSD is its established efficacy in treating disorders commonly comorbid with PTSD, such as depression[31-33] and panic disorder.[34-36] In the current study, sertraline demonstrated a significant efficacy advantage over placebo in the treatment of PTSD (Table 3), although specific measures of panic or anxiety disorders were not obtained.

Research for PTSD treatment is still in its infancy. The slow progress in identifying effective drug therapies specific to PTSD may be partly due to a residual conceptual bias that sees PTSD as an extension of a normative stress reaction. Unease at the use of drug treatment to facilitate normal coping is appropriate. Yet, as Yehuda and McFarlane argued,[49] PTSD is very different from a typical or even intense stress reaction: the high chronicity, comorbidity, and severity, as well as PTSD-related alterations in underlying neurochemical and neuroendocrine substrates are uite distinct from what are observed in normative stress reactions. In this view, trauma may be a necessary but by no means sufficient condition for the development of syndromic PTSD. Ongoing research is attempting to identify psychological and neurobiological vulnerability factors that may place a person who has experienced trauma at risk for the development of PTSD.[49]

This investigation and a companion study[50] provide strong support for the efficacy of sertraline in the acute treatment of PTSD. Additional research is needed to determine whether subgroups of PTSD patients might respond preferentially to drug or behavioral treatments or might optimally benefit from combination therapy. Finally, what constitutes an ade uate therapeutic trial and whether and when patients with PTSD might benefit from long-term treatment are also issues that await further research.

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