

# Multicenter, Double-blind Comparison of Sertraline and Placebo in the Treatment of Posttraumatic Stress Disorder

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**Background:** Posttraumatic stress disorder (PTSD) is a common illness associated with significant disability. Few large, placebo-controlled trials have been reported.

**Methods:** Outpatients with a *DSM-III-R* diagnosis of moderate-to-severe PTSD were randomized to 12 weeks of double-blind treatment with either sertraline (N=100) in flexible daily doses in the range of 50 to 200 mg or placebo (N=108). Primary outcome measures consisted of the Clinician-Administered PTSD Scale (CAPS-2) total severity score, the patient-rated Impact of Event Scale (IES), and the Clinical Global Impression-Severity (CGI-S) and -Improvement (CGI-I) ratings.

**Results:** Mixed-effects analyses found significantly steeper improvement slopes for sertraline compared with placebo on the CAPS-2 ( $t=2.96, P=.003$ ), the IES ( $t=2.26,$

$P=.02$ ), the CGI-I score ( $t=3.62, P<.001$ ), and the CGI-S score ( $t=4.40, P<.001$ ). An intent-to-treat end-point analysis found a 60% responder rate for sertraline and a 38% responder rate for placebo ( $\chi^2_1=8.48, P=.004$ ). Sertraline treatment was well tolerated, with a 9% discontinuation rate because of adverse events, compared with 5% for placebo. Adverse events that were significantly more common in subjects given sertraline compared with placebo consisted of insomnia (35% vs 22%), diarrhea (28% vs 11%), nausea (23% vs 11%), fatigue (13% vs 5%), and decreased appetite (12% vs 1%).

**Conclusion:** The results of the current study suggest that sertraline is a safe, well-tolerated, and significantly effective treatment for PTSD.

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SINCE ITS original diagnostic formulation in 1980, considerable research has been conducted on posttraumatic stress disorder (PTSD). This research has established that PTSD is common, with a lifetime prevalence in the range of 7% to 12% and a 2:1 female-to-male ratio<sup>1-3</sup>; chronic, with a median time-to-recovery in the range of 3 to 5 years<sup>1,4</sup>; and has high comorbidity, with a 6-fold increased risk, compared with community norms, of major depression, a 3-fold increased risk of alcoholism or substance abuse, an approximately 4-fold increased risk of panic disorder or agoraphobia, and an estimated suicide attempt rate of approximately 20%.<sup>1,5,6</sup> Posttraumatic stress disorder is also associated with significant functional and psychosocial disability<sup>7,8</sup> and notable increases in physical symptoms and health care utilization.<sup>5,9-11</sup>

Currently, it is estimated that the most widely used treatments for PTSD in the community consist of counseling,<sup>12</sup> symptomatic treatment of associated in-

somnia and anxiety with benzodiazepines or low-dose antidepressants, or self-medication with alcohol.<sup>13</sup>

An increasing number of studies have been conducted in an attempt to establish effective treatments for PTSD. Initial studies have reported promising results for cognitive and behavioral treatments,<sup>13-16</sup> but confirmation of the efficacy of cognitive or behavior therapies for PTSD awaits the results of additional well-designed clinical trials, with blinded and parallel control groups, and with larger sample sizes.

Controlled trials testing the efficacy of drug therapy for PTSD are sparse. A comprehensive review published in 1992<sup>17</sup> found few placebo-controlled clinical trials, and limited efficacy for the few that were reported, although phenelzine, and, to a lesser extent, imipramine and amitriptyline, were more effective than placebo in combat veterans with PTSD.<sup>18,19</sup> Since that time, 2 equivocal or negative double-blind, placebo-controlled clinical trials have been published of brofaromine (since discontinued).<sup>20,21</sup> Re-

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## SUBJECTS AND METHODS

### SUBJECTS

The subjects were male and female outpatients 18 years and older who met *DSM-III-R*<sup>36</sup> criteria for a primary diagnosis of PTSD as determined by part 1 of the Clinician-Administered PTSD Scale (CAPS-1). A minimum 6-month duration of PTSD illness was required (exceeding the 1-month minimum required by *DSM-III-R*), as well as a total score of 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. All subjects were required to be free of psychotropic medication for at least 2 weeks before beginning treatment, or 5 weeks for fluoxetine. Female participation was contingent on a negative  $\beta$ -human chorionic gonadotropin pregnancy test and stable use of a medically accepted form of contraception. Exclusion criteria included (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; (3) alcohol or substance abuse or dependence 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 adequate trial; and (6) current use of any medication (except occasional use of chloral hydrate) with clinically significant psychotropic properties. Subjects were not permitted to participate in cognitive-behavioral therapy during the trial, but were permitted to attend ongoing psychotherapy or counseling that was initiated at least 3 months before randomization.

Subjects were recruited from current clinical populations and through the use of flyers, newspaper advertisements, and radio advertisements. The study was approved by the institutional review board, or by a national institutional review board, at each of the 12 collaborating centers. The benefits and risks of study participation were fully explained to each subject, and written informed consent was obtained.

### STUDY DESIGN

The study was a double-blind, randomized, flexible-dose comparison of sertraline and placebo for the treatment of PTSD in outpatients. After a 1-week, single-blind, placebo run-in period, subjects were randomized, using computer-generated random numbers, to 12 weeks of double-blind, parallel treatment with either matched placebo or sertraline. Sertraline treatment was initiated at 25 mg per day for 1 week, with flexible daily dosing thereafter in the range of 50 to 200 mg, based on clinical response and tolerability.

Study visits took place at baseline and at the end of study treatment weeks 1, 2, 3, 4, 6, 8, 10, and 12, or at the time of discontinuation if before week 12.

### ASSESSMENTS

#### Baseline

Subjects were evaluated for study entry by a research clinician (physician, psychologist, or psychiatric nurse) with experience in conducting psychopharmacology research. The current severity of PTSD symptoms was determined by a psychiatric history and by the CAPS-1, a structured interview that includes the *DSM-III-R* PTSD diagnostic criteria.<sup>37,38</sup> A structured clinical interview based on *DSM-III-R*<sup>39</sup> was performed to evaluate the presence of comorbid psychiatric illness. A medical history, physical examination, and routine laboratory tests were performed. Baseline PTSD symptoms 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,<sup>37,38</sup> which is an investigator-completed assessment instrument that rates the frequency and intensity of PTSD symptoms on separate 5-point severity scales; the Impact of Event Scale (IES),<sup>40,41</sup> a 15-item subject-rated instrument that assesses intrusion

sults of 2 placebo-controlled studies have also been published, each with approximately 50 outpatients, suggesting efficacy for fluoxetine in PTSD in civilians, but not in combat veterans.<sup>22,23</sup>

A potential therapy for PTSD must effectively treat the core symptoms of the disorder,<sup>24</sup> consisting of reexperiencing (intrusive thoughts, nightmares, flashbacks, images, or memories); phobic avoidance of trauma-related situation; emotional numbing (flattened affect or detachment and/or loss of interest and motivation); and hyperarousal (startle reactions, poor concentration, irritability and jumpiness, insomnia, and hypervigilance). Optimally, a candidate therapy should also be effective in restoring normal functioning and improving symptoms associated with common psychiatric comorbidity. Sertraline would seem to be such a drug, with demonstrated efficacy in the treatment of depression<sup>25-28</sup> and panic disorder,<sup>29-31</sup> and preliminary evidence of efficacy in alcoholism,<sup>32,33</sup> as well as uncontrolled pilot studies suggesting efficacy in PTSD.<sup>34,35</sup> We report here results of a large, multisite, placebo-controlled, double-blind trial

designed to test the efficacy and tolerability of sertraline in the treatment of PTSD.

## RESULTS

### SUBJECT CHARACTERISTICS

Two hundred eight subjects were randomly assigned to sertraline or placebo, of whom 98 sertraline-treated subjects and 104 placebo-treated subjects were available for at least 1 postbaseline efficacy assessment, and so constituted the intent-to-treat sample.

Demographic and clinical characteristics for the subject sample are shown in **Table 1**. The only significant difference between the 2 treatment groups in any of the baseline variables was the smaller percentage of males in the sertraline group. Women constituted the majority of the sample. The age of subjects ranged from 18 to 69 years, with 75% younger than 45 years. An analysis by sex revealed no significant differences in any of the baseline variables. The difference observed in Table 1 be-

and avoidance symptoms on a 4-point severity scale; and the CGI-S and CGI-Improvement (CGI-I) scales.<sup>42</sup> Assessment of primary outcome measures was performed at baseline (except CGI-I) and at every study visit.

Secondary outcome measures consisted of (1) the 17-item Davidson Trauma Scale (DTS),<sup>43,44</sup> which rates frequency and severity of DSM-III-R–defined PTSD symptoms on separate 5-point scales; (2) the 24-item Hamilton Depression Rating Scale (HAM-D)<sup>45</sup>; (3) the Hamilton Anxiety Rating Scale (HAM-A)<sup>46</sup>; (4) DSM-III-R–defined clusters of the CAPS-2, IES, and the DTS: reexperiencing/intrusion, avoidance/numbing, and arousal; (5) individual global ratings (social functioning, occupational functioning, overall improvement, and severity of illness) from the CAPS-2, rated from 0 to 4; (6) CAPS-2 items that rate associated features of PTSD in terms of frequency and intensity, including guilt and hopelessness; and (7) the Pittsburgh Sleep Quality Index.<sup>47</sup> The CAPS-2 and DTS were administered at every study visit, while the HAM-D, HAM-A, and Pittsburgh Sleep Quality Index were administered at baseline and study end point only.

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 dose, stop and start dates, and reason for use. Laboratory assessments (eg, clinical chemistry, hematology, urinalysis) were performed initially at screen, and repeated at weeks 6 and 12 (or at the time of study discontinuation). A physical examination and electrocardiogram were performed at screen and at week 12 (or at the time of discontinuation if before week 12).

Compliance was monitored by pill counts of returned medication; subjects were counseled if found to be noncompliant.

## DATA ANALYSIS

Baseline characteristics were compared between the treatment groups using analysis of variance or  $\chi^2$  (for sex). The

main efficacy analyses were performed using change from baseline to end point during the 12-week treatment period. The efficacy variables were analyzed via analysis of covariance, with the effects of site and treatment in the model and baseline scores as the covariate. For the CGI-I scale, there is no baseline value and therefore an analysis of variance was performed on the end-point score with site and treatment in the model. Treatment  $\times$  site interactions were examined in all analyses, but none were significant and therefore interaction terms were deleted from all further analyses. Statistical analyses were performed on SAS, version 6.12. All statistical tests were 2-sided and performed at the .05 level of significance.

Clinical response to treatment was defined in 2 ways: (1) a 30% or greater decrease in the CAPS-2 scores and (2) a CGI-I rating of 1 (very much improved) or 2 (much improved). The post hoc decision to add the CAPS-2 criteria was based on the recommendation of an expert consensus panel (unpublished data, Pfizer Inc, New York, NY, March 4, 1998), which suggested that a symptomatic improvement criterion was a necessary component of determining response status. Analysis of responder rates employed a Mantel-Haenszel  $\chi^2$  statistic stratifying by site.

The incidence of adverse events, the percentage of subjects who discontinued because of adverse events, and the incidence of clinically significant laboratory abnormalities were compared between treatment groups using Fisher exact test. Changes in vital signs (blood pressure, heart rate, and body weight) were compared for the 2 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.<sup>48</sup> 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 in curves between the 2 treatment groups.

tween the duration of illness, and the time since the traumatic event seems to be attributable to several factors, including presence in an individual of more than 1 trauma and delayed onset of the full diagnosis. Consistent with many other PTSD treatment studies in civilian populations, the most common trauma category was physical/sexual assault (**Table 2**).

## EFFICACY

At baseline there were no significant between-treatment group differences on any of the efficacy variables. Treatment with sertraline resulted in significantly greater improvement compared with placebo in all 4 primary efficacy measures that had been defined a priori (**Table 3**). The benefit of sertraline on the 2 PTSD severity scales (the CAPS-2 and the IES) was confirmed both by global (CGI) measures of severity and improvement, as well as by the subject-rated scale, the DTS. An analysis of completers showed similar trends in favor of the sertraline-treated group, but failure to reach significance was prob-

ably attributable to the reduced statistical power caused by the 22% dropout rate.

**Figure 1** shows the results of a Kaplan-Meier analysis of time to response using the post hoc consensus criteria CGI-I score of 2 or less and 30% or more reduction from baseline in the CAPS-2 total score. As can be seen, significantly ( $\chi^2_1=8.48$ ,  $P=.004$ ) more sertraline-treated subjects were classified as responders at end point compared with placebo subjects.

**Figure 2** shows the change scores on both the clinician-rated CAPS-2 total severity measure (A), and on the subject-rated DTS (B) estimated from mixed-effects analyses plotted over the 12-week course of study treatment. As can be seen, a significantly steeper improvement slope was observed with sertraline compared with placebo on both measures ( $t_{1379}=-2.96$ ,  $P=.003$  for CAPS-2, and  $t_{1377}=-3.45$ ,  $P<.001$  for DTS). Additional mixed-effects analyses also found significantly steeper improvement slopes in favor of sertraline for the IES ( $t_{1375}=-2.26$ ,  $P=.02$ ), for the CGI-I score ( $t_{1178}=-3.62$ ,  $P<.001$ ), and for CGI-S ( $t_{1380}=-4.40$ ,  $P<.001$ ).

**Table 1. Demographic and Clinical Characteristic of Study Subjects Diagnosed as Having Posttraumatic Stress Disorder (PTSD)**

Patient Variable	Sertraline (N = 100)	Placebo (N = 108)	Test Statistic	P
<b>Subjects Diagnosed as Having PTSD</b>				
Female, %	84	72	$\chi^2 = 4.18$	.04
Age, y, mean $\pm$ SD	37.6 $\pm$ 11.1	36.6 $\pm$ 10.1	$t = 0.58$	.56
Race, %			$\chi^2 = 0.06$	
Black	13	11		
White	83	84		
Other	4	5		.81
Duration of illness, y, mean $\pm$ SD	11.7 $\pm$ 11.1	12.8 $\pm$ 12.4	$t = 0.06$	.51
Time from traumatic event, y, mean $\pm$ SD	18.3 $\pm$ 12.8	18.5 $\pm$ 15.5	$t = 0.04$	.97
Current major depression, %	40	40	$\chi^2 < 0.01$	.98
Current anxiety disorder, %	23	18	$\chi^2 = 0.94$	.33
History of alcohol dependence/abuse, %	24	27	$\chi^2 = 0.02$	.64
History of substance dependence/abuse, %	14	18	$\chi^2 = 0.50$	.46
<b>Frequency of Index Traumatic Event by Category, %</b>				
Physical or sexual assault	64	60	$\chi^2_3 = 2.83$	.42
Seeing someone hurt or die	11	12		
Serious accident/fire/injury	8	15		
Being in a war or combat*	5	5		
Natural disaster*	0	1		
Other event*	12	7		

\*Because of the small sample sizes, the bottom 3 categories are grouped for the purpose of the analysis.

Analysis of the core PTSD symptom cluster subscales showed a similar, although less consistently significant, advantage for sertraline at study end point on both clinician- and subject-rated measures (Table 3). The mean percentage of reduction from baseline in the reexperiencing/intrusion symptom cluster was 50% and 53%, respectively, on the CAPS-2 and IES, a 47% reduction in the avoidance/numbing symptom cluster on both the CAPS-2 and IES, and a 40% reduction on the arousal symptom cluster of the CAPS-2.

A treatment  $\times$  sex analysis was performed on the CAPS-2 change score and was not found to be significant. The number of males in the study (46 males [22%]) was too small to perform meaningful analyses, especially since there were other sex-related confounding factors (eg, differential trauma type) that would have to be accounted for.

Among the secondary efficacy measures (Table 3), moderate improvement was observed on the HAM-D and HAM-A, but there was no significant difference from placebo. Similarly, sertraline improved sleep quality as measured by the Pittsburgh Sleep Quality Index, but not significantly more than placebo.

## EFFECT OF STUDY TREATMENT ON FUNCTIONAL AND PSYCHOSOCIAL MEASURES

Social functioning, as measured by the global rating on the CAPS-2, showed significantly greater improvement on sertraline (2.6  $\pm$  0.8 to 1.2  $\pm$  1.1) compared with placebo (2.7  $\pm$  0.9 to 1.7  $\pm$  1.1;  $t = 2.48$ ;  $P = .01$ ). Similarly, the CAPS-2 rating of occupational functioning also showed significantly greater improvement for sertraline compared with placebo, with an adjusted mean change score, respectively, of 0.9 vs 0.6 ( $t = 2.24$ ;  $P = .02$ ). These results should be interpreted with caution because the social and occupational ratings on CAPS-2 have been less well validated than the symptom severity ratings.

## TREATMENT AND TOLERABILITY

The mean  $\pm$  SD daily dose of sertraline at study end point for completers was 146.3  $\pm$  49.3 mg. Sertraline was generally well tolerated. Subjects reported the following rates of adverse events for sertraline and placebo, respectively: insomnia (35% vs 22%,  $P = .04$ ); headache (33% vs 24%,  $P = .17$ ); diarrhea (28% vs 11%,  $P = .003$ ); nausea (23% vs 11%,  $P = .03$ ); drowsiness (17% vs 11%,  $P = .24$ ); nervousness (14% vs 8%,  $P = .27$ ); fatigue (13% vs 5%,  $P = .05$ ); decreased appetite (12% vs 1%,  $P = .001$ ); dry mouth (10% vs 7%,  $P = .45$ ); and vivid dreams (10% vs 4%,  $P = .10$ ).

Thirty-two subjects discontinued sertraline treatment (30%) compared with 35 subjects who discontinued placebo treatment (27%). The primary reason cited for discontinuation of sertraline and placebo, respectively, was as follows: adverse events (9.1% vs 4.7%); withdrawal of consent (6.1% vs 3.8%); lost to follow-up (5.1% vs 10.4%); protocol violation (2.0% vs 4.7%); laboratory abnormality (2.0% vs 0%); insufficient therapeutic response (0% vs 4.7%); and miscellaneous other reasons (2.0% vs 1.9%). Two sertraline subjects discontinued prematurely because of mild elevations in aspartate aminotransferase and alanine aminotransferase values. There were no serious electrocardiographic or laboratory abnormalities during the course of the study, nor were there any significant differences between the 2 treatment groups in the incidence of electrocardiographic or laboratory abnormalities.

There were no significant differences between the sertraline group and the placebo group in terms of changes in vital signs, with the exception of sitting heart rate. Sertraline-treated subjects showed a decrease from baseline to end point, while placebo-treated subjects showed an increase (-2.7 and 1.71 beats/min, respectively;  $t = 2.68$ ;  $P = .007$ ). However, no subjects in either group showed a clinically significant change in heart rate or blood pressure.

## COMMENT

The results of the present study indicate that sertraline is an effective acute treatment for PTSD. This investigation, together with a companion study<sup>49</sup> that was also positive on all primary outcome measures, represent

**Table 2. Effect of Study Treatment on Primary and Secondary Efficacy Measures in Subjects Diagnosed as Having Posttraumatic Stress Disorder (PTSD), Change From Baseline to End Point\***

Efficacy Variables	Sertraline (N = 98)	Placebo (N = 104)	t Test Statistic	P
<b>Primary Outcome Measures</b>				
CAPS-2 total score, mean ± SD				
Baseline	73.9 ± 16.2	73.5 ± 16.1	2.02	.04
Change	-33.0 ± 2.4	-26.2 ± 2.3		
IES total score, mean ± SD				
Baseline	38.5 ± 15.6	40.0 ± 14.5	2.36	.02
Change	-19.2 ± 1.5	-14.1 ± 1.5		
CGI-Severity, mean ± SD				
Baseline	4.6 ± 1.0	4.6 ± 0.9	2.09	.04
Change	-1.3 ± 0.1	-1.0 ± 0.1		
CGI-Improvement, mean ± SD	2.3 ± 0.1	2.8 ± 0.1	2.46	.01
<b>Secondary Outcome Measures</b>				
Davidson PTSD Scale total score, mean ± SD				
Baseline	74.5 ± 26.9	73.8 ± 26.2	3.08	.002
Change	-32.3 ± 2.8	-20.0 ± 2.7		
HAM-D, 21-item total score, mean ± SD				
Baseline	21.7 ± 8.2	21.2 ± 8.3	0.97	.33
Change	-7.7 ± 1.0	-6.3 ± 1.0		
HAM-A total score, mean ± SD				
Baseline	20.0 ± 7.9	19.3 ± 7.4	1.12	.26
Change	-7.8 ± 0.8	-6.4 ± 0.9		
Pittsburgh Sleep Quality Scale, mean ± SD				
Baseline	11.7 ± 3.7	12.1 ± 3.8	0.75	.45
Change	-3.0 ± 0.5	-2.5 ± 0.5		

\*CAPS-2 indicates Clinician-Administered PTSD Scale, Part 2; IES, Impact of Event Scale; CGI, Clinical Global Impression Scale; HAM-D, Hamilton Rating Scale for Depression; and HAM-A, Hamilton Rating Scale for Anxiety.

the largest randomized placebo-controlled trials published to date on the treatment of PTSD.

Acute treatment with sertraline in the present study resulted in a clinically significant mean reduction from baseline in the range of 45% to 50% on the 2 primary measures of overall PTSD symptom severity, the CAPS-2 and the IES (Table 3). On both the CAPS-2 and the IES, approximately 70% of the improvement in PTSD symptoms occurred during the first 4 weeks of treatment. The mixed-effects analysis confirmed that the improvement observed over the 12 weeks of sertraline treatment was consistently greater than placebo across both of these primary outcome measures (Figure 2).

The severity of the 3 PTSD core symptom clusters also improved with sertraline treatment (Table 4), but the improvement was less consistently significant on the clinician-rated CAPS-2 when compared with placebo. In contrast, the subject-rated DTS and IES consistently detected significantly greater efficacy advantage for sertraline over placebo on all 3 PTSD symptom clusters, suggesting that subject self-rating scales may be more sensitive measures for evaluating treatment effects in PTSD than clinician ratings.

Paralleling improvement in PTSD symptoms, global measures of social functioning and occupational functioning also showed rapid and significant improvement. In a similar 12-week, double-blind study of sertraline and placebo using the Quality of Life, Enjoyment, and Satisfaction Questionnaire,<sup>49,50</sup> sertraline-treated subjects were improved on measures of social relationships, leisure activities, ability to function daily, living situation, ability

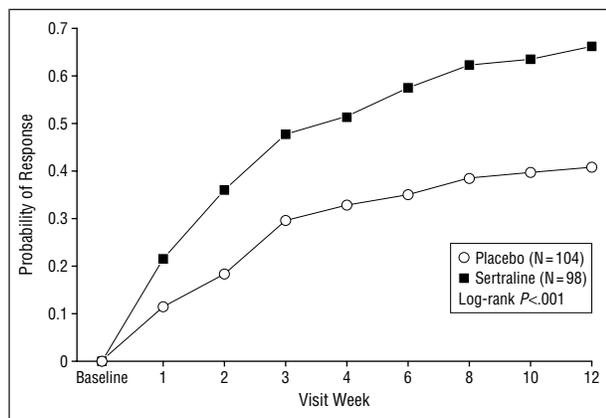
to get around physically, and ability to work after 12 weeks of treatment. The results from the CAPS-2 function items in this study indicate similar improvements. Posttraumatic stress disorder has been characterized as one of the most functionally debilitating disorders, and small symptom improvements leading to resumed daily activities, such as driving or taking elevators, can have a profound impact on family and work life.

Although sertraline, relative to placebo, improved the symptoms of PTSD and its associated features, no significant differences between sertraline and placebo were found on either the HAM-A or HAM-D change scores at end point. Subjects with primary diagnoses of major depression or most anxiety disorders were excluded from the current trial. However, mild-to-moderate levels of both anxiety and depression were reported by most subjects at baseline, as evidenced by mean HAM-A and HAM-D scores near 20. The lack of differential improvement in anxiety and depressive symptoms, therefore, was unlikely to be a function of limited room for change on these scales because of low baseline scores. It is possible that chronic, subsyndromic anxious and depressive symptoms associated with PTSD may require a longer course of therapy. However, this is speculation, and arguing against this hypothesis is the larger, and earlier-onset, treatment effect found for sertraline treatment of subjects with dysthymic disorder and double depression.<sup>27,28</sup> The relative lack of acute antidepressant effect in the current subject sample makes it unlikely that an antidepressant response is a necessary precondition for the efficacy of sertraline in the treatment of PTSD.

**Table 3. Effect of Study Treatment on Posttraumatic Stress Disorder (PTSD) Symptom Cluster Subscales in Subjects Diagnosed as Having PTSD, Change From Baseline to End Point**

PTSD Symptom Clusters, Subscales of Primary Measures	Sertraline (N = 98)	Placebo (N = 104)	t Test Statistic	P
<b>Reexperiencing/Intrusion</b>				
CAPS-2, mean ± SD				
Baseline	15.1 ± 5.6	15.3 ± 6.3	1.05	.29
Change	-7.5 ± 0.7	-6.5 ± 0.7		
IES, mean ± SD				
Baseline	18.0 ± 8.6	19.6 ± 8.1	2.21	.03
Change	-9.6 ± 0.8	-6.9 ± 0.8		
DTS, mean ± SD				
Baseline	14.8 ± 7.5	15.1 ± 7.6	2.18	.03
Change	-6.7 ± 0.8	-4.4 ± 0.8		
<b>Avoidance/Numbing</b>				
CAPS-2, mean ± SD				
Baseline	31.4 ± 9.0	31.2 ± 8.9	2.41	.02
Change	-14.7 ± 1.2	-10.6 ± 1.2		
IES, mean ± SD				
Baseline	20.5 ± 9.8	20.5 ± 9.2	1.98	.05
Change	-9.6 ± 0.9	-7.1 ± 0.9		
DTS, mean ± SD				
Baseline	30.3 ± 13.2	30.4 ± 12.4	2.96	.003
Change	-12.8 ± 1.3	-7.2 ± 1.3		
<b>Arousal/Hyperarousal</b>				
CAPS-2, mean ± SD				
Baseline	27.3 ± 6.6	27.0 ± 6.3	1.55	.12
Change	-10.8 ± 0.9	-8.9 ± 0.9		
DTS, mean ± SD				
Baseline	28.2 ± 10.3	28.3 ± 10.2	2.69	.007
Change	-11.8 ± 1.1	-7.8 ± 1.0		
<b>Associated Features</b>				
CAPS-2, mean ± SD				
Baseline	25.1 ± 10.0	23.8 ± 10.3	2.56	.01
Change	-10.5 ± 1.0	-6.8 ± 1.0		

\*CAPS-2 indicates Clinician-Administered PTSD Scale, Part 2; IES, Impact of Event Scale; and DTS, Davidson Trauma Scale.

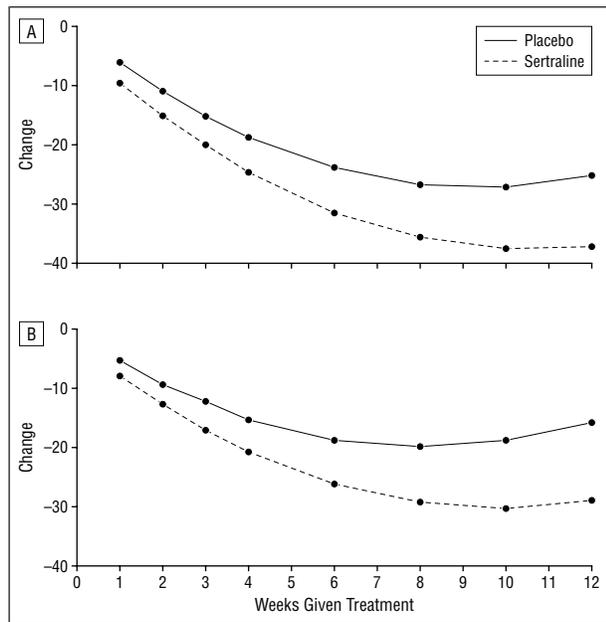


**Figure 1.** Kaplan-Meier time-to-response analysis. The responder is defined by scoring 1 or 2 on the Clinical Global Impression-Improvement Scale, and a decrease of 30% or more in the total score from baseline on part 2 of the Clinician-Administered Posttraumatic Stress Disorder Scale.

Sertraline was well tolerated, with 9% of sertraline-treated subjects, compared with 5% of placebo-treated subjects, discontinuing treatment during the 12-week study period because of adverse events. There were no differences between the sertraline group and the placebo group in the incidence of laboratory abnormali-

ties, and no clinically significant changes in vital signs or electrocardiogram were found for any subjects.

The study as conducted has several limitations. First, study entry criteria excluded patients with a current history of alcohol or substance abuse. Other study entry criteria required a moderate-or-higher level of current symptom severity. The generalizability of our study results to patients in the community suffering from PTSD must be made with an awareness of potential differences between the 2 populations. Another limitation is that the study was not powered to evaluate the influence of potentially important clinical variables, such as sex, type of trauma, duration of illness, or presence of comorbidity on treatment response. We plan to pool the data from the current study with data from a study of very similar design<sup>49</sup> to undertake exploratory analyses of some of these issues. Another limitation of the current study is that it provides no information on the longer-term effects of sertraline in consolidating the improvement in PTSD symptoms obtained during acute therapy and in sustaining this level of improvement (ie, in preventing relapse). The results of a recently completed 12-month treatment study should provide data on this topic (J.R.T.D., P. Londberg, MD, T. Pearlstein, MD, K. T. Brady, MD, PhD, B.O.R., J. Bell, MD, R. Mad-



**Figure 2.** Results of random regression analyses comparing the effects of a 12-week treatment with sertraline and placebo. A, Mean change score estimate from a random regression analysis on part 2 of the Clinician-Administered Posttraumatic Stress Disorder Scale ( $t_{1379} = -2.96$ ,  $P = .003$ ). B, Mean change scores from a random regression analysis on the Impact of Event Scale ( $t_{1377} = -3.45$ ,  $P = .0006$ ).

dock, MD, M. T. Hegel, PhD, and G.M.F., unpublished data, 2000).

How do the results of the current study compare with previously conducted PTSD treatment research? First, in terms of indexing the results obtained here against previous results, it should be noted that the placebo response rate in the current study (38%) was comparable with rates reported in previously published placebo-controlled drug therapy studies.<sup>20-23</sup> Placebo response rates in these studies range as high as 62% (in the study reported by Connor et al<sup>23</sup>) when no symptom severity reduction criteria were applied. The current study joins a growing number of well-designed studies of drug therapy<sup>20-23</sup> and cognitive or behavioral therapy<sup>13-16</sup> that have reported efficacy in the treatment of PTSD, but there are still relatively few placebo-controlled studies with larger sample sizes available. For example, among psychosocial treatments, cognitive-behavior therapy is the most well established as a treatment, but the largest and most positive recent study testing its efficacy<sup>13</sup> had only 20 subjects at end point in the exposure-alone treatment group and 19 subjects at end point in the exposure-plus-cognitive-therapy treatment group. Confidence in the positive results of this study were further complicated by the fact that subjects in each group were concurrently being treated with antidepressants (17% in the former and 42% in the latter treatment group), as well as by other significant between-treatment group differences, most notably a duration of illness that ranged from 23 to 61 months.

The importance of the current study is increased by the relative dearth of large-scale controlled treatment studies, which is surprising given the high prevalence,<sup>1-3</sup> chronicity,<sup>1,4</sup> comorbidity,<sup>1,5,6</sup> and disability<sup>7,8</sup> associated with

PTSD. The similarly positive results of a second study<sup>49</sup> provide further evidence suggesting that sertraline is a safe, well-tolerated, and, compared with placebo, significantly effective treatment for this long-neglected public health problem.

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