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

Jonathan R. T. Davidson, MD; Barbara O. Rothbaum, PhD; Bessel A. van der Kolk, MD; Carolyn R. Sikes, PhD; Gail M. Farfel, PhD

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 endpoint analysis found a 60% responder rate for sertraline and a 38% responder rate for placebo (χ² = 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 (33% 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.

Arch Gen Psychiatry. 2001;58:485-492

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; chronic, with a median time-to-recovery in the range of 3 to 5 years; 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%. Posttraumatic stress disorder is also associated with significant functional and psychosocial disability and notable increases in physical symptoms and health care utilization.

Currently, it is estimated that the most widely used treatments for PTSD in the community consist of counseling, symptomatic treatment of associated insomnia and anxiety with benzodiazepines or low-dose antidepressants, or self-medication with alcohol.

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, 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 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. Since that time, 2 equivocal or negative double-blind, placebo-controlled clinical trials have been published of brofaromine (since discontinued).
SUBJECTS AND METHODS

SUBJECTS

The subjects were male and female outpatients 18 years and older who met DSM-III-R 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 β-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, 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.37,38 A structured clinical interview based on DSM-III-R 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-2,37,38 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),40,41 a 15-item subject-rated instrument that assesses intrusion.

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.42 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),41,44 which rates fre-
quency and severity of DSM-III-R–defined PTSD symptoms
on separate 5-point scales; (2) the 24-item Hamilton Depres-
sion Rating Scale (HAM-D)16; (3) the Hamilton Anxiety Rat-
ing Scale (HAM-A)46; (4) DSM-III-R–defined clusters of the
CAPS-2, IES, and the DTS: reexperiencing/intrusion, avoid-
ance/numbing, and arousal; (5) individual global ratings (so-
cial functioning, occupational functioning, overall improve-
ment, 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 hope-
lessness; and (7) the Pittsburgh Sleep Quality Index.47 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 ef-
facts that were spontaneously reported or observed were re-
corded 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 chemis-
try, hematology, urinalysis) were performed initially at screen,
and repeated at weeks 6 and 12 (or at the time of study discon-
tinuation). A physical examination and electrocardio-
gram 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 re-
turned medication; subjects were counseled if found to be
noncompliant.

DATA ANALYSIS

Baseline characteristics were compared between the treat-
ment groups using analysis of variance or χ² (for sex). The
main efficacy analyses were performed using change from
baseline to end point during the 12-week treatment pe-
riod. 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. Treatment in the model.
Treatment×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, ver-
sion 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 cri-
terias was based on the recommendation of an expert con-
sensus panel (unpublished data, Pfizer Inc, New York, NY,
March 4, 1998), which suggested that a symptomatic im-
provement criterion was a necessary component of deter-
mining response status. Analysis of responder rates em-
ployed a Mantel-Haenszel χ² statistic stratifying by site.

The incidence of adverse events, the percentage of sub-
jects who discontinued because of adverse events, and the
incidence of clinically significant laboratory abnor-
malities 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 longitudi-
nal data.48 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 lin-
ear and quadratic terms of duration of treatment. We ex-
amined the response curves for each treatment group and
compared the difference in curves between the 2 treat-
ment groups.

EFFICACY

At baseline there were no significant between-treatment
group differences on any of the efficacy variables. Treat-
ment with sertraline resulted in significantly greater im-
provement 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 com-
pleters 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 analy-
sis of time to response using the post hoc consensus cri-
teria 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 (χ² = 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 clin-
ician-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 treat-
ment. As can be seen, a significantly steeper improve-
ment slope was observed with sertraline compared with
placebo on both measures (t₁379 = −2.96, P = .003 for
CAPS-2, and t₁377 = −3.45, P < .001 for DTS). Additional
mixed-effects analyses also found significantly steeper im-
provement slopes in favor of sertraline for the IES
(t₁375 = −2.26, P = .02), for the CGI-I score (t₁178 = −3.62,
P < .001), and for CGI-S (t₁380 = −4.40, P < .001).
Table 1. Demographic and Clinical Characteristic of Study Subjects Diagnosed as Having Posttraumatic Stress Disorder (PTSD)

<table>
<thead>
<tr>
<th>Patient Variable</th>
<th>Sertraline (N = 100)</th>
<th>Placebo (N = 108)</th>
<th>Test Statistic</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects Diagnosed as Having PTSD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female, %</td>
<td>84</td>
<td>72</td>
<td>χ² = 4.18</td>
<td>.04</td>
</tr>
<tr>
<td>Age, y, mean ± SD</td>
<td>37.6 ± 11.1</td>
<td>36.6 ± 10.1</td>
<td>t = 0.58</td>
<td>.56</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
<td></td>
<td>χ² = 0.06</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>13</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>83</td>
<td>84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>5</td>
<td></td>
<td>.81</td>
</tr>
<tr>
<td>Duration of illness, y</td>
<td>11.7 ± 11.1</td>
<td>12.8 ± 12.4</td>
<td>t = 0.06</td>
<td>.51</td>
</tr>
<tr>
<td>Time from traumatic event, y</td>
<td>18.3 ± 12.8</td>
<td>18.5 ± 15.5</td>
<td>t = 0.04</td>
<td>.97</td>
</tr>
<tr>
<td>Current major depression, %</td>
<td>40</td>
<td>40</td>
<td></td>
<td>.98</td>
</tr>
<tr>
<td>Current anxiety disorder, %</td>
<td>23</td>
<td>18</td>
<td>χ² = 0.94</td>
<td>.33</td>
</tr>
<tr>
<td>History of alcohol dependence/abuse, %</td>
<td>24</td>
<td>27</td>
<td>χ² = 0.02</td>
<td>.64</td>
</tr>
<tr>
<td>History of substance dependence/abuse, %</td>
<td>14</td>
<td>18</td>
<td>χ² = 0.50</td>
<td>.46</td>
</tr>
</tbody>
</table>

 Frequency of Index Traumatic Event by Category, %

<table>
<thead>
<tr>
<th>Event</th>
<th>Sertraline</th>
<th>Placebo</th>
<th>Test Statistic</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical or sexual assault</td>
<td>64</td>
<td>60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seeing someone hurt or die</td>
<td>11</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious accident/fire/other</td>
<td>8</td>
<td>15</td>
<td>χ² = 2.83</td>
<td>.42</td>
</tr>
<tr>
<td>Being in a war or combat*</td>
<td>5</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Natural disaster*</td>
<td>0</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other event*</td>
<td>12</td>
<td>7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*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 endpoint on both clinician- and subject-rated measures (Table 3). The mean percentage of reduction from baseline in the re-experiencing/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×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±0.8 to 1.2±1.1) compared with placebo (2.7±0.9 to 1.7±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±SD daily dose of sertraline at study endpoint for completers was 146.3±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 that was also positive on all primary outcome measures, represent...
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, sertraline-treated subjects were improved on measures of social relationships, leisure activities, ability to function daily, 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. 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 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**

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

*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.*
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 abnormalities, 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 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-

### 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

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

*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.](http://archgenpsychiatry.com)
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, 1,3 chronicity, 1,7 comorbidity, 1,5 and disability 7 associated with PTSD. The similarly positive results of a second study 49 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.

Accepted for publication December 21, 2000.
Financial support for this study was provided by Pfizer Inc, New York, NY.

Presented at the American College of Neuropsychopharmacology, Kamuela, Hawaii, December 1997; and at the International Society for Traumatic Stress Studies, Washington, DC, November 1998.

The investigators in this study and the corresponding sites at which the study was conducted were Jessy Colah, MD, and Renaka Tank, MD, Adult and Geriatric Outpatient Services, Brooklyn, NY; Kathleen Brady, PhD, MD, Institute of Psychiatry, Charleston, SC; Paul Newhouse, MD, Fletcher Allen Healthcare, Burlington, VT; Barbara O. Rothbaum, PhD, The Emory Clinic, and the Department of Psychiatry and Behavioral Sciences, Atlanta, GA; Hisham Hafez, MD, and Phillip Santora, MD, Charter Brookside Hospital and Research Department, C. Brookside Hospital, Nashua, NH; Peter Londborg, MD, Seattle Clinical Research Center, Seattle, Wash; Teri Pearlstein, MD, Butler Hospital, Providence, RI; Bessel van der Kolk, MD, PhD, Human Resource Institute, Brookline, Mass; Wayne Phillips, MD, PhD, Boulder PTSD Center, Boulder, Colo; Katherine Shear, MD, University of Pittsburgh School of Medicine, Pittsburgh, Pa; Richard Weisler, MD, Raleigh, NC; William Patterson, MD, Birmingham Research Group Inc, Birmingham, Ala; Phebe Tucker, MD, University of Oklahoma Health Sciences Center, Oklahoma City.

Corresponding author and reprints: Jonathan R. T. Davidson, MD, Department of Psychiatry and Behavioral Sciences, Anxiety and Traumatic Stress Program, Duke University Medical Center, Box 3812, Durham, NC 27710.

Fig 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 (t1377=–2.96, P = .003). B, Mean change scores from a random regression analysis on the Impact of Event Scale (t1375=–3.45, P = .0006).

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. 20-23 Placebo response rates in these studies range as high as 62% (in the study reported by Connor et al 23) when no symptom severity reduction criteria were applied. The current study joins a growing number of well-designed studies of drug therapy 20-23 and cognitive or behavioral therapy 13-16 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 recent study testing its efficacy 13 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.

REFERENCES

7. Kimelring R, Callhoun KS. Somatic symptoms, social support, and treatment-


