Sertraline Treatment of Posttraumatic Stress Disorder: Results of 24 Weeks of Open-Label Continuation Treatment

Peter D. Londborg, M.D.; Mark T. Hegel, Ph.D.; Susanna Goldstein, M.D.; David Goldstein, M.D.; Jonathan M. Himmelhoch, M.D.; Richard Maddock, M.D.; William M. Patterson, M.D.; Jeffrey Rausch, M.D.; and Gail M. Farfel, Ph.D.

Background: Posttraumatic stress disorder (PTSD) is typically associated with a high degree of chronicity, comorbidity, and psychosocial disability. The efficacy of sertraline in the acute treatment of PTSD has been confirmed based on the results of 2 large, placebo-controlled studies, but almost no prospective long-term treatment studies have been reported.

Method: One hundred twenty-eight patients who completed 12 weeks of double-blind, placebo-controlled, acute-phase treatment for DSM-III-R–defined PTSD with sertraline were continued into a 24-week open-label continuation phase. Efficacy was evaluated using the endpoint change in the 17-item Clinician Administered PTSD Scale Part 2 (CAPS-2) severity score, the 15-item patient-rated Impact of Event Scale, and the Clinical Global Impressions-Improvement and -Severity of Illness scales as primary outcome measures. Treatment response was defined as ≥ 30% decrease in the CAPS-2 total severity score (compared with acute-phase baseline score) and a Clinical Global Impressions-Improvement score of 1 or 2.

Results: Ninety-two percent of acute-phase responders maintained their response during the full 6 months of continuation treatment. In addition, 54% of acute-phase nonresponders converted to responder status during continuation therapy. Over the 36-week course of acute and continuation therapy, 20% to 25% of the improvement in the CAPS-2 severity score occurred during the continuation phase. Sertraline was well tolerated, with 8.6% of patients discontinuing due to adverse events. A high pretreatment CAPS-2 score (> 75) predicted a longer time to response and a greater likelihood that response occurred after 12 weeks of acute treatment.

Conclusion: The acute efficacy of sertraline is sustained in the vast majority of patients, and at least half of nonresponders to acute treatment will eventually respond to continued treatment.

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Reprint requests to: Peter D. Londborg, M.D., Summit Research Network, Washington Division, 901 Boren, Suite 1800, Seattle, WA 98104.

Traumatic stress is increasingly being recognized as a ubiquitous exogenous pathogen[1,2] that is implicated in the etiology of a broad range of affective, anxiety, eating, and personality disorders. In addition, it is specifically associated with the development of posttraumatic stress disorder (PTSD), an illness with a lifetime prevalence reported to be in the range of 5% to 12%, making it one of the most prevalent of all psychiatric disorders.[3,4]

PTSD frequently is a chronic illness, with a median time to recovery in the range of 3 to 5 years and lasting much longer than that in the more severe or chronic cases.[3,5] High PTSD chronicity is accompanied by increased health-related problems and levels of disability and impairment in quality of life.[6–11]

Recent research has begun to establish the efficacy of pharmacologic treatments of PTSD, particularly the selective serotonin reuptake inhibitors (SSRIs). Preliminary evidence of efficacy in PTSD, based on open-label treatment studies or on small, placebo-controlled pilot studies, has been presented for fluoxetine, sertraline, nefazodone, paroxetine, and fluvoxamine.[12–17] More recently, the efficacy of sertraline in the acute treatment of PTSD has been confirmed based on the results of 2 large, placebo-controlled studies.[18,19] The pharmacologic trials of SSRIs have ranged from 5 to 12 weeks in duration. No published study to date has reported efficacy and safety results beyond 12 weeks.

The current study reports the results of 24 weeks of open-label continuation sertraline treatment in 128 patients

who had completed 12 weeks of double-blind, placebo-controlled, acute-phase treatment for PTSD with sertraline. The blinding to acute-phase treatment was maintained throughout the 24-week continuation study. This cohort of patients treated with sertraline was studied to examine the effect of longer-duration pharmacologic treatment of PTSD, a topic on which there are no previously published data. We were interested in whether the initial acute response to sertraline would be sustained over 6 months of continuation treatment and to what extent patients who had shown an acute response would continue to improve, both symptomatically and in terms of quality of life. Since the optimal duration of acute pharmacologic treatment for PTSD has not yet been established, we were also interested in examining what percentage of patients who did not respond to the initial 12 weeks of acute sertraline treatment would convert to responder status when a longer duration of treatment was provided. Lastly, we attempted to identify possible baseline demographic and clinical variables that might be associated with a delayed treatment response.

Patients who had been treated with placebo in the acute phase (N = 123) were also offered open-label sertraline treatment, and the results for these patients will be the subject of a later report, along with the results of a relapse prevention study in which patients were subsequently randomly reassigned to sertraline or placebo.

METHOD

The present investigation reports an analysis of data from a study conducted at 24 centers in the United States. Patients who completed 1 of 2 identical randomized, double-blind, 12-week trials comparing sertraline with placebo were eligible to enter a 24-week open-label continuation study within 3 days of their last visit in the acute study. To preserve the blind from the acute study, all patients were discontinued from their acute-phase study medication (sertraline or placebo) prior to initiating open-label study treatment with a daily dose of 25 mg of sertraline. At the end of the first week of continuation treatment, the daily dose of sertraline was increased to 50 mg; patients who failed to demonstrate a satisfactory clinical response and who were tolerating the medication could undergo additional dose titration in 50-mg-per-week increments to a maximum daily dose of 200 mg.

Study Patients

Patients who enrolled in the current 24-week study were male and female outpatients at least 18 years of age who had completed 1 of two 12-week, double-blind, placebo-controlled, flexible-dose studies of sertraline in the acute treatment of PTSD. At baseline of the acute studies, patients had to have met criteria for a principal diagnosis of PTSD as determined by the Structured Clinical Interview for DSM-III-R (SCID)[20] and the Clinician Administered PTSD Scale Part 1.[21,22] A minimum 6-month duration of PTSD symptoms was required (exceeding the 1-month minimum required by DSM-III-R) as well as a total severity score ≥ 50 on the Clinician Administered PTSD Scale Part 2 (CAPS-2)[21,22] at the end of a 2-week placebo run-in period. As such, the patients in the study were at least moderately ill. Patients were excluded if they had (1) current or past history of bipolar, schizophrenic, or other psychotic disorder; (2) current organic mental disorder, factitious or malingering, or primary diagnosis of major depression, obsessive-compulsive disorder (OCD), or other anxiety disorders; (3) alcohol or substance dependence or abuse in 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; or (5) intolerance or hypersensitivity to sertraline or nonresponse to a previous adequate medication trial. Concomitant psychotropic therapy was prohibited during the trial with the exception of chloral hydrate for sleep (not more than 2 nights per week). Cognitive-behavioral therapy was not permitted during the trial, and other forms of psychotherapy could not be initiated or terminated during the trial. Although there is no credible evidence from well-controlled studies for the efficacy of any other form of psychotherapy in the treatment of PTSD, it should be cautioned that some of the treatment effects of the current study might conceivably derive from psychotherapy received outside the study by a small minority of patients, even though the psychotherapy treatment had failed to achieve efficacy prior to the beginning of the current study.

The current article presents an analysis that is limited to patients who had received sertraline in the acute phase of study treatment. Patients who completed the acute-treatment study were permitted to enroll in the current long-term trial whether or not they had responded to acute treatment as long as there were no clinically significant laboratory, electrocardiogram (ECG), or medical abnormalities identified at the time of the physical examination performed at the end of 12 weeks of acute treatment. Female patients were also required to have a negative β-human chorionic gonadotropin (HCG) pregnancy test at week 12 and to continue to use medically acceptable birth control.

The study was approved by the institutional review board (IRB) at each of the 24 collaborating centers or by a national IRB. The benefits and risks of study participation were fully explained to each patient, including potential risk of adverse events, and a new written informed consent statement was obtained for the extension study.

Efficacy and Tolerability Assessments

During the 24 weeks of open-label treatment, patients were evaluated and rated weekly for the first 4 weeks and then every 2 weeks thereafter.

The primary outcome measures for the study consisted of 2 PTSD scales: (1) the 17-item total severity score of the CAPS-2,[21,22] a 30-item investigator-completed scale that rates both the frequency and intensity of PTSD symptoms on separate 5-point scales; and (2) the Impact of Event Scale (IES),[23,24] a 15-item patient-completed scale that rates intrusion and avoidance symptoms on a 6-point severity scale. In addition, the Clinical Global Impressions-Improvement scale (CGI-I),[25] an investigator-rated global assessment, and the CGI-Severity of Illness scale (CGI-S),[25] an investigator-rated assessment of global severity of illness, were utilized as primary outcome measures and were assessed with reference to the pretreatment baseline score from the acute-treatment studies.

Secondary outcome measures consisted of (1) the patient-rated 17-item Davidson Trauma Scale (DTS),[26,27] which rates the 17 DSM-III-R–defined PTSD symptoms on a 5-point frequency scale and a 5-point severity scale; (2) the investigator-rated 24-item Hamilton Rating Scale for Depression (HAM-D)[28]; (3) a validated short form of the patient-rated Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)[29]; (4) subscales of the CAPS-2, IES, and DTS that report the severity of the 3 PTSD symptom clusters reexperiencing/intrusion, avoidance/numbing, and hyperarousal; and (5) subscales of the CAPS-2 that measure associated features and functional impairment.

The DTS was completed by patients at every assessment visit. The HAM-D and the Q-LES-Q were completed at baseline of the acute phase, at baseline of the open-label continuation study, and at the end of week 24 or at the time of study discontinuation if prior to week 24.

Safety evaluations included assessment at each study visit of weight, sitting blood pressure, and pulse rate. Side effects that were observed or spontaneously reported 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, start and stop dates, and reason for use. Laboratory assessments (e.g., clinical chemistry, hematology, and urinalysis) were performed at the baseline of the open-label study and repeated at weeks 6 and 24 (or at the time of study discontinuation). A physical examination and a 12-lead ECG were performed at the open-label study baseline and at week 24 (or at the time of study discontinuation).

Compliance was monitored by counts of returned medication, and patients were counseled if found to be noncompliant.

Statistical Methods

Patients who took at least 1 dose of study medication during this study and for whom safety data were obtained were included in the safety analysis. All safety-evaluable patients with available postbaseline efficacy data were included in the intent-to-treat analysis of efficacy. The primary efficacy parameters in the study were the CAPS-2 17-item total severity score, IES total score, and CGI-S and CGI-I ratings. For changes from baseline to the endpoint, summaries are presented for intent-to-treat patients randomly assigned to the sertraline treatment group in the feeder studies. Changes in the primary and secondary efficacy parameters from baseline of the feeder studies to endpoint of the current study were summarized for patients randomly assigned to sertraline in the feeder studies.

Responder status was defined as at least a 30% decrease in the CAPS-2 total severity score (as compared with the baseline of the 2 acute-phase "feeder" studies) and a CGI-I score of 1 or 2. Response rates were further investigated by comparing proportions of responders at the baseline of the current study (end of feeder study) and at the endpoint of the current study using the McNemar test (2-sided). This analysis was performed for patients treated with sertraline in the feeder studies.

All treatment-emergent adverse events occurring up to 7 days after the last dose of study drug were categorized according to World Health Organization terminology and tabulated regardless of their assessed severity or relationship to study drug. Adverse events in this study were defined as treatment emergent if onset occurred during the current study; if the adverse event continued from the feeder studies, it was considered ongoing and was not included in the summaries.

Analysis of time to response was conducted for patients treated with sertraline in the feeder studies to assess the importance of a wide range of potential predictors. Relative risk ratios were calculated based on a Cox proportional hazards regression model that included effects for gender, age, duration of PTSD illness, history of childhood trauma, presence of multiple traumas, history of drug abuse, history of alcohol abuse, current depression comorbidity, current anxiety disorder comorbidity, and stratified (high vs. low) baseline values of CAPS-2, HAM-D, and Q-LES-Q scores. Proportional hazard regression model was fit in a forward stepwise fashion.

RESULTS

Patient Sample and Disposition

Two hundred fifty-two patients entered the 24-week open-label sertraline treatment phase; 128 (50.8%) had been treated with sertraline, while 124 (49.2%) had been treated with placebo during the acute double-blind phase of the 2 feeder studies. The 128 patients who had been treated initially with sertraline are the subject of the current article. Seventy-four percent of the 128 sertraline-treated patients were women (mean ± SD age = 39.8 ± 10.5 years; mean ± SD duration of PTSD illness = 11.4 ± 11.3 years); 26% of the patients were men (mean ± SD age = 41.2 ± 9.8 years; mean ± SD duration of PTSD illness = 16.9 ± 12.2 years). Eighty-seven percent of sertra-

Table 1. Frequency of Types of Index Traumatic Events[a] (all randomly assigned patients)

	Women (N = 95)		Men (N = 33)	
Event	N	%	N	%
Natural disaster	0	0.0	0	0.0
Serious accident, injury, or fire	6	6.3	2	6.1
Physical or sexual assault	63	66.3	11	33.3
Seeing someone get hurt or die	9	9.5	9	27.3
Being in a war or combat	1	1.1	8	24.2
Other event	16	16.8	3	9.1

[a]Index event defined as trauma that is the primary focus of current posttraumatic stress disorder symptomatology.

line-treated patients in the current study sample were white. Comorbidity was common at the time of entry into the acute-treatment studies: 23.2% of women and 18.2% of men suffered from a SCID-diagnosed Axis I anxiety disorder; 34.7% of women and 60.6% of men suffered from SCID-diagnosed Axis I major depressive or dysthymic disorder; while no Axis I diagnosis was identified in 54.7% of women and 36.4% of men (note that patients may have had more than 1 comorbid Axis I diagnosis).

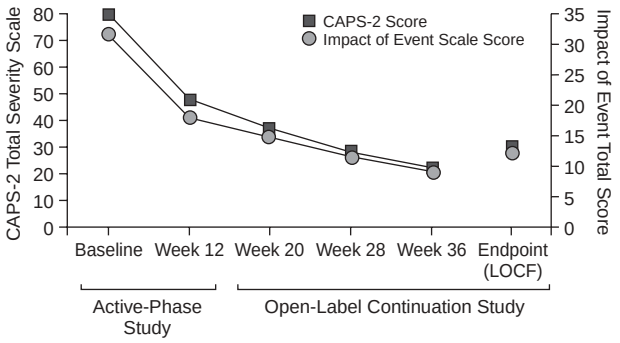
The distribution of traumatic events varied by gender (Table 1); almost two thirds of women reported sexual or physical assault as the precipitating trauma, while for men the type of trauma was more evenly distributed.

Efficacy

The effect of study treatment on the range of PTSD symptomatology was measured by 2 clinician-rated scales, the CAPS-2 and the IES (Figure 1), and by the patient-rated DTS (Table 2). As can be seen in Figure 1, patients continued to show progressive improvement in both clinician-rated PTSD scales over the course of continuation therapy. The majority of the improvement observed during continuation-phase treatment (weeks 12–36) was contributed by patients who had not achieved responder status by the end of 12 weeks of acute treatment. For example, mean ± SD improvement on the CAPS-2 total severity score during open-label treatment was –25.1 ± 22.6 for acute-phase nonresponders versus –4.0 ± 20.0 for acute-phase responders. Similarly, mean ± SD improvement on the IES was –13.5 ± 14.9 for nonresponders versus –2.9 ± 9.5 for responders.

Table 2 summarizes the improvement observed for continuation patients for the CGI-I as well as for the DTS and other secondary outcome measures. The results confirm the benefit of continuation sertraline treatment for an additional 24 weeks after 12 weeks of acute treatment. For example, 41% of all the improvement in HAM-D total scores observed across 9 months of treatment occurred during continuation treatment. Similarly, 31% of the improvement in quality of life occurred during the continuation phase.

Figure 1. The Effect of Continuation Treatment With Open-Label Sertraline on Core Symptoms of Posttraumatic Stress Disorder (N = 128)[a]



[a]Abbreviations: CAPS-2 = Clinician Administered PTSD Scale Part 2, LOCF = last observation carried forward.

Figure 2 shows the extent to which continuation sertraline treatment was able to sustain initial improvement among patients who had achieved responder criteria by the end of acute treatment. Fully 92% of acute-phase responders (68/74) were able to sustain their initial response. The figure also shows that 54% of patients (28/52) who had failed to meet responder criteria during the acute phase became responders during continuation treatment. Forty-nine percent of the patients who converted to responder status did so within the first 6 weeks of continuation treatment.

Predictors of Longer Time to Response

A Cox regression analysis was performed for time to response for the subgroup of 128 patients who received sertraline in the acute treatment phase and entered continuation treatment. Twelve variables were in the model, including gender, age, duration of illness, baseline CAPS-2 severity score, baseline depression severity (HAM-D total score), history of childhood trauma, number of traumas, history of alcohol or substance abuse, current depression or anxiety disorder comorbidity, and degree of baseline impairment in quality of life.

The only variable that was identified as a significant ($p = .008$) predictor of longer time to response was having a high baseline CAPS-2 severity score. For patients with a baseline CAPS-2 severity score > 75, the risk ratio for not achieving responder status by the end of 12 weeks of acute treatment was 0.6 (i.e., 60% lower likelihood of responding).

Tolerability

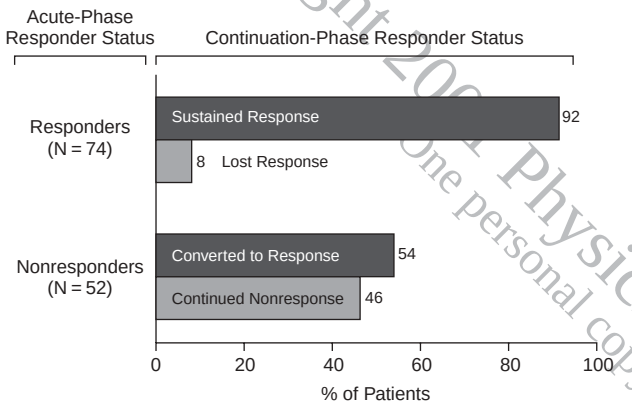
For the group of patients who were randomly assigned to sertraline in the acute study, the mean ± SD daily dose of sertraline at endpoint of the 24-week open-label study was 128.7 ± 68.9 mg. Overall, 77 of the 128 patients

Table 2. Effect of 12 Weeks of Acute Treatment and 24 Weeks of Continuation Treatment With Sertraline on Clinical Outcome[a]

	Acute-Phase Baseline (N = 128)		End of Acute Phase (Week 12) (N = 128)		End of Continuation Phase (Week-36 Completers) (N = 75)		End of Continuation Phase (LOCF endpoint) (N = 126)	
Scale	Mean	SD	Mean	SD	Mean	SD	Mean	SD
CGI-I	NA	NA	2.4	1.2	1.6	0.8	1.9	1.1
CGI-S	4.5	0.7	3.2	1.2	2.5	1.1	2.8	1.3
Davidson Trauma Scale	73.4	23.6	41.5	30.3	23.5	24.1	30.0	26.8
HAM-D total score	21.2	6.1	13.1	9.1	7.4	6.5	9.1	8.2
Q-LES-Q	53.5	11.4	66.6	16.8	72.4	14.2	70.7	14.9

[a]Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D = Hamilton Rating Scale for Depression, LOCF = last observation carried forward, Q-LES-Q = Quality of Life Satisfaction and Enjoyment Questionnaire.

Figure 2. Continuation-Phase Outcome Based on Acute-Phase Response Category



(60.2%) completed the study. Among the 39.8% of patients who discontinued prematurely, reasons cited for discontinuation included lost to follow-up, 16 patients (12.5%); adverse events, 11 patients (8.6%); withdrawal of consent, 6 patients (4.7%); protocol violation, 5 patients (3.9%); insufficient clinical response, 2 patients (1.6%); laboratory abnormality, 2 patients (1.6%); and miscellaneous other reasons, 9 patients (7.0%). Among the patients who discontinued prematurely, 52% (27/51) met responder criteria at the time of study discontinuation.

Treatment-emergent adverse events reported in at least 10% of patients during 24 weeks of open-label sertraline treatment included the following (moderate-to-severe treatment-related adverse event rates are shown in parentheses): upper respiratory infection, 24.2% (0.0%); headache, 22.7% (4.7%); insomnia, 17.2% (3.1%); diarrhea, 16.4% (2.3%); nausea, 12.5% (3.9%); dry mouth, 10.9% (3.9%); fatigue, 10.9% (3.1%); malaise, 10.9% (0.0%); dizziness, 10.2% (1.6%); and, for males, ejaculatory failure, 12.1% (3.0%). There were no significant differences in the incidence of adverse events by gender. There were 7 instances of serious adverse events in 5 patients during the 24-week trial, but none of them were attributed to sertraline treatment.

No serious abnormalities in ECG, laboratory tests, or vital signs were attributed by study investigators to sertraline during 24 weeks of treatment. There was a mean increase of 2.46 mm Hg in systolic blood pressure and a mean increase of 0.60 mm Hg in diastolic blood pressure, and heart rate decreased by 0.63 beats per minute. Body weight increased by a mean of 1.7 lb (0.8 kg).

DISCUSSION

We report here the results of 24 weeks of open-label continuation treatment with sertraline in patients completing 12 weeks of double-blind, placebo-controlled acute sertraline treatment. Two key findings of this open-label trial are that the majority of patients (92%) who responded to 12 weeks of acute sertraline treatment maintained their response during the next 6 months of treatment. In addition, of the 41% of patients who had not responded at the end of acute treatment, more than half (Figure 2) achieved responder status during subsequent open-label treatment.

To our knowledge, no continuation treatment data have been published in patients diagnosed with PTSD that might cross-validate or serve as a comparison for these data. Results from studies of continuation treatment in patients diagnosed with major depression suggest a sustained efficacy of approximately 80%.[30,31] Sustained efficacy during continuation treatment of chronic forms of major depression (in which the illness duration is comparable to the duration reported in the current sample) has been reported in the range of 75% to 80%.[32] Sustained efficacy during continuation treatment of OCD has been reported to range from 70% to 80%.[33] The ability of continuation treatment with sertraline to sustain the acute response in PTSD patients would appear to equal or exceed the efficacy reported for continuation treatment with antidepressants for most other affective and anxiety disorders.

Another key finding from this study is that patients continue to experience improvement in their PTSD symptoms during weeks 12 to 36 of treatment. The data shown in Figure 1 and Table 2 suggest progressive improvement among patients: approximately 20% to 25% of the total improvement in PTSD symptoms over 36 weeks of treatment occurred during weeks 12 to 36. This temporal pattern of response held not only for symptomatic measures

such as the CAPS-2 and the IES but also for the CGI scales and the Q-LES-Q. Given the chronicity of the current patient sample, with a median duration of illness of approximately 16 years, it is interesting that improvement in quality of life occurs so rapidly, with approximately 70% of the Q-LES-Q improvement recorded during the acute 12-week treatment period. These results, though, are consistent with the results from acute-treatment studies of patients suffering from both depression and panic disorder.[34] Additional studies of Q-LES-Q response might be useful to further understand the specificity of these results.

Another question addressed by the current data is whether continued sertraline treatment, beyond the initial 12 weeks, might yield significant clinical benefit in patients who were acute-phase nonresponders. Fifty-four percent of initial nonresponders converted to responder status during continuation treatment (Figure 2). There was a 25-point mean improvement in the CAPS-2 score and a 14-point mean improvement in the IES total score among acute-phase nonresponders. These results suggest that approximately one third of patients suffering from PTSD may require a longer acute treatment period in order to achieve a clinically significant response. Overall, the combined response rate (acute responders plus converted responders) was 74% at the endpoint of the 24-week study.

The possibility of delayed therapeutic response creates a clinical decision-making dilemma—whether to continue a patient on sertraline for an additional 4 to 8 weeks who has not responded after 8 to 12 weeks of initial treatment. The results of the Cox regression analysis did not yield a useful clinical profile of patients who might respond if the acute treatment were longer in duration, with the exception of higher baseline CAPS-2 severity scores. This latter finding is intriguing, since treatment studies of men with combat-related PTSD frequently report baseline CAPS-2 scores that are significantly higher than the baseline scores of civilian PTSD studies. These combat PTSD studies have generally been negative, although none of these studies has ever provided treatment for longer than 8 to 12 weeks.[12,16,17,35]

The major limitation of the current study stems from its open-label design with no random assignment and no double-blinded comparison with placebo. On the one hand, this makes it more likely that the results of this study may be generalizable to actual clinical practice. On the other hand, we cannot be as confident of inferences about efficacy based on the data, since we have no control for nonspecific factors that might contribute to improvement, such as doctor-patient contact or expectancy-of-improvement effects. As a consequence, the current study should be viewed as a preliminary investigation. A further limitation of the study is the relatively small sample size due, in part, to an attrition rate of 39.8%. It should be noted, though, that the observed attrition rate is consistent with rates of attrition reported in most other long-term treatment studies. Such studies require a significant and rather inflexible commitment from participants, and many succumb to what might be characterized as "study fatigue." This latter suggestion is supported by the fact that 52% of patients were responders at the time of premature study discontinuation.

CONCLUSION

The results of previous double-blind, placebo-controlled treatment studies[18,19] have confirmed the efficacy of sertraline as an acute treatment for moderate-to-severe PTSD in civilians. The current open-label continuation phase sertraline study provides evidence that the acute efficacy of sertraline is sustained in the vast majority of patients and that at least half of the initial nonresponders to acute treatment will eventually respond to continued treatment. High baseline severity of PTSD symptomatology (CAPS-2 score > 75) significantly predicted a longer time to response. This suggests that the time course of treatment response in patients with chronic, moderate-to-severe PTSD may more closely parallel response times seen in OCD than in major depression. Finally, improvement in PTSD symptomatology is accompanied by rapid and marked improvement in patient quality of life and perceived ability to function. This is especially important in an illness such as PTSD whose psychological, behavioral, and medical consequences have been shown to be so devastating.

Drug names: fluoxetine (Prozac), fluvoxamine (Luvox), nefazodone (Serzone), paroxetine (Paxil), sertraline (Zoloft).

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