Paroxetine in the Treatment of Chronic Posttraumatic Stress Disorder: Results of a Placebo-Controlled, Flexible-Dosage Trial

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Background: The objective of this double-blind, placebo-controlled study was to investigate the efficacy and safety of paroxetine in outpatients with posttraumatic stress disorder (PTSD).

Method: Male and female outpatients 18 years and older who met DSM-IV criteria for PTSD and had baseline scores of 50 or greater on the Clinician Administered PTSD Scale (CAPS-2) were randomly assigned to treatment with paroxetine (20–50 mg/day) or placebo for 12 weeks. The primary efficacy variables were the change from baseline to the 12-week endpoint in the CAPS-2 total score and the proportion of responders on the Clinical Global Impressions-Global Improvement scale (CGI-I). Additional key outcome measures were the change from baseline in the reexperiencing, avoidance/numbing, and hyperarousal scores of the CAPS-2 and in the total scores of the Treatment Outcome PTSD Scale and the patient-rated Davidson Trauma Scale and Sheehan Disability Scale (SDS). Depressive symptoms were assessed with the Montgomery-Asberg Depression Rating Scale. The proportion of patients achieving response and remission was also determined.

Results: 307 patients constituted the intent-to-treat population. At week 12, compared with the placebo group (N = 156), the paroxetine group (N = 151) showed significantly greater reduction of PTSD symptoms on both of the primary and all of the secondary outcome measures. Significantly greater improvement on the CAPS-2 total score was observed for paroxetine compared with placebo from week 4 ($p < .05$), and significantly greater proportions of paroxetine-treated patients achieved response ($p < .001$) and remission ($p = .008$) by week 12. The improvement in PTSD symptoms was similar in male and female patients. Functional improvement at the study endpoint was significantly greater ($p < .05$) in the paroxetine group in all 3 domains of the SDS (work, social life, family life). Treatment with paroxetine was well tolerated, with the frequency and type of adverse events recorded for the paroxetine group corresponding to the known safety profile of this medication.

Conclusion: Paroxetine in doses of 20 to 50 mg once daily is effective as a treatment for chronic PTSD. Improvement is obtained for all 3 symptom clusters (reexperiencing, avoidance/numbing, hyperarousal) and is associated with significant reduction in disability after 12 weeks of treatment.

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According to DSM-IV, posttraumatic stress disorder (PTSD) results from exposure to a traumatic event in which an individual experienced, witnessed, or was confronted with actual or threatened death or serious injury, or a threat to physical integrity to self or others. PTSD encompasses 3 symptom clusters: (1) persistent reexperiencing of the trauma, (2) avoidance behavior associated with a feeling of detachment and emotional numbness, and (3) symptoms of increased autonomic arousal.[1]

Community-based epidemiologic studies indicate a lifetime prevalence of PTSD ranging from 8% to 12%,[2,3] with at-risk individuals (victims of criminal violence, survivors of civilian disasters, combat veterans) showing prevalence rates from 4% to 30%.[4–6] Recent studies confirm that the impairment caused by PTSD is comparable to or greater than that of other psychiatric disorders. Persons with PTSD often experience marital, occupational, and health problems and are disproportionate consumers of health care resources.[7–9] More than 80% of those with PTSD will develop during their lifetime at least one other psychiatric disorder, most frequently major depression.[2] The risk of suicide attempts among persons with anxiety disorders is highest for PTSD sufferers, and, relative to

the general population, PTSD is associated with a 6-fold greater risk of suicide attempt.[9,10]

During the past decade, evidence from various research groups has led to a growing recognition of a biological basis for PTSD. In particular, alterations in brain neurochemistry involving the hypothalamic-pituitary-adrenocortical (HPA) axis and the neurotransmitters serotonin and norepinephrine have been linked to the presence of PTSD symptoms.[11,12] Despite this evidence, to date few controlled studies of pharmacologic treatments of this disorder have been conducted. In the first placebo-controlled trials, which involved small patient samples, only modest efficacy was found for the tricyclic antidepressants (TCAs) imipramine and amitriptyline and moderate efficacy for the monoamine oxidase inhibitor (MAOI) phenelzine,[13–15] with contradictory results reported for the MAO-A inhibitor brofaromine (not available in the United States).[16,17] In 2 controlled trials, the benzodiazepines alprazolam and clonazepam did not significantly affect the symptoms of PTSD.[18,19] A pilot study investigating the effects of lamotrigine found that this anticonvulsant improved intrusion and avoidance, but not hyperarousal symptoms, to a greater extent than placebo.[20]

More recent investigations have focused on the selective serotonin reuptake inhibitors (SSRIs), which as a class have proven efficacy in treating depression and a number of anxiety disorders. These medications are generally considered to be more convenient in administration and safer in overdose than the TCAs and to lack the abuse potential of the benzodiazepines. The first placebo-controlled study with an SSRI, which investigated treatment over 5 weeks in small civilian and veteran patient samples, demonstrated that fluoxetine is effective in alleviating emotional numbing and hyperarousal symptoms in a mixed population of combat veteran and civilian PTSD sufferers.[21] However, this study did not show a statistically significant effect on avoidance or reexperiencing symptoms. Of note in this investigation, combat veterans as a group did not respond, which suggests that it may be difficult to draw general conclusions from a patient sample that includes a large proportion of treatment-resistant subjects. In a 12-week study, a significantly greater proportion of patients treated with fluoxetine than with placebo achieved response as measured by a global outcome scale based on the Clinical Global Impressions scale (CGI).[22] A subsequent analysis of secondary patient- and clinician-rated outcome measures from this study suggested that fluoxetine may be efficacious for all symptom clusters of PTSD.[23] Most recently, the results of two 12-week studies using the Clinician Administered PTSD Scale (CAPS-2)[24,25] as a primary outcome measure show that, overall, the SSRI sertraline is more effective than placebo as a treatment for PTSD.[26,27] However, as was the case for fluoxetine, using this recognized clinical assessment, significant reduction of the intensity and frequency of reexperiencing symptoms by sertraline was not shown, although in the study by Davidson et al.[27] efficacy across all 3 symptom clusters was demonstrated by other outcome measures.

Clinical research conducted over the last 10 years has shown that the SSRI paroxetine not only is an effective antidepressant,[28,29] but also possesses a broad spectrum of anxiolytic activity, having demonstrated efficacy in the treatment of social anxiety disorder,[30] obsessive-compulsive disorder (OCD),[31] panic disorder,[32] and generalized anxiety disorder.[33] Preliminary clinical work has also indicated that paroxetine is effective in treating the symptoms of PTSD: in a 12-week open-label trial, Marshall et al.[34] observed substantial improvement in all 3 PTSD symptom clusters as measured by a clinician-rated version of the Davidson Trauma Scale (DTS), with two thirds of the patients achieving the response criteria of "very much improved" or "much improved" on the Clinical Global Impressions-Global Improvement scale (CGI-I). A randomized comparison of paroxetine and cognitive-behavioral therapy showed clinically relevant improvement in PTSD symptoms with both treatments (> 30% reduction in baseline CAPS-2 score) after 12 weeks.[35] On the basis of this previous research, a 12-week, multicenter study investigating the efficacy of paroxetine for the treatment of PTSD was conducted. The results of this study are reported here.

METHOD

This was a randomized, double-blind, parallel-group, placebo-controlled flexible-dose study of outpatients with chronic PTSD. The study was conducted at 37 centers in the United States and Canada.

Patient Selection

Male and female patients at least 18 years of age were included in the study at the initial (screening) assessment if they satisfied the DSM-IV criteria for chronic PTSD as determined by the Mini-International Neuropsychiatric Interview[36] and the Clinician Administered PTSD Scale, Part 1 (CAPS-1).[24,25] The CAPS is a validated structured interview administered by a trained clinician and is designed to quantify the frequency and intensity of each of the 17 DSM-IV–defined PTSD symptoms. The CAPS-1 assesses for current and lifetime diagnosis of PTSD, while the CAPS-2 is used to evaluate the change in symptom severity during treatment. Based on clinical research with the CAPS over the past decade, the authors of this instrument have proposed 5 severity score ranges for interpreting the total CAPS score: > 80 = extreme PTSD symptomatology, 60 to 79 = severe, 40 to 59 = threshold to moderate, 20 to 39 = subthreshold to moderate, 0 to 19 = asymptomatic or few PTSD symptoms.[25]

Subjects with comorbid bipolar disorder, dissociative disorder, or any psychotic disorder were not eligible for entry into this study. Patients with comorbid mood and anxiety disorders were considered eligible, under the condition that PTSD was considered the primary diagnosis (i.e., the focus of attention or the need for treatment). Following a 1-week placebo run-in phase, patients were reassessed at the baseline visit and excluded from the study if they scored less than 50 (of a possible 136) on the first 17 items of the CAPS-2. Also excluded were patients who were involved in litigation or were receiving disability payments because of any psychiatric disorder, who had received formal psychotherapy or electroconvulsive therapy in the 12 weeks prior to the initial assessment, or who met DSM-IV criteria for alcohol/drug dependence or abuse within the preceding 6 months. Psychotropic medications were discontinued prior to the baseline assessment, with the period of washout being 1 week for most antidepressants, 2 weeks for hypnotics and sedatives, 4 weeks for fluoxetine and MAOIs, and 12 weeks for depot neuroleptics. Women of childbearing potential practicing a clinically accepted method of contraception were included, while women who had a positive pregnancy test at screening or who were lactating were excluded. Psychoactive herbal medications (e.g., St. John's wort) were not allowed during the study.

The protocol for this study was approved by the institutional review board at each of the participating centers. Written informed consent was obtained from each patient before any study-specific procedures were carried out.

Study Flow

Following the screening assessment and the 1-week placebo run-in period, patients still eligible according to the inclusion and exclusion criteria at the baseline assessment were randomly assigned 1:1 to either paroxetine or placebo for a 12-week treatment period. Patients randomly assigned to paroxetine started treatment at 20 mg daily and remained at this dosage for the first 2 weeks. After week 2, the paroxetine dosage could be increased according to the judgment of the investigating physician every 2 weeks by 10 mg/day up to 50 mg/day. During the treatment period, a single dosage reduction (because of physical illness or an adverse event) was allowed for patients taking at least 30 mg/day of paroxetine (or placebo equivalent). Chloral hydrate was permitted in doses up to 1000 mg for a maximum of 3 nights per week during the first week of double-blind treatment.

Efficacy Measures and Safety Assessments

The primary outcome measures were (1) the change from baseline to the week-12 endpoint in the CAPS-2 total score and (2) the proportion of responders on the CGI-I, with response being defined as a score of 1 ("very much improved") or 2 ("much improved"). Secondary outcome measures were the change from baseline in the total scores of the patient-rated DTS[37] and the clinician-rated Treatment Outcome PTSD Scale (TOP-8).[38] In order to evaluate improvement in the 3 symptom clusters of PTSD (reexperiencing, avoidance/numbing, hyperarousal), the change from baseline in the corresponding symptom cluster scores of the CAPS-2 and DTS was investigated. Functional impairment was assessed using the patient-rated Sheehan Disability Scale (SDS).[39] The severity of comorbid depressive symptoms was evaluated with the clinician-rated Montgomery-Asberg Depression Rating Scale (MADRS).[40] Finally, consistent with Weathers et al.,[25] a CAPS-2 score of less than 20 (asymptomatic or few PTSD symptoms) was defined as remission ("symptom resolution and resolution of functional impairment," as formulated by Ballenger[41]).

Following the baseline assessment, the CGI-I was administered at weeks 1 and 2 and biweekly thereafter; the CAPS-2 and DTS, at weeks 4, 8, and 12; the SDS, at weeks 6 and 12; and the TOP-8 and MADRS, at week 12. For patients discontinuing the study, these outcome measures were recorded at the time of dropout, if possible. Safety assessments conducted at the screening and endpoint visits (or upon study discontinuation) included a complete physical examination, electrocardiogram, and laboratory evaluation (clinical chemistry with serum pregnancy test, hematology, urinalysis). Sitting heart rate and blood pressure were also documented at each scheduled visit. Observed and reported adverse experiences were recorded with respect to time of onset, severity, action taken, and outcome.

Data Analysis

The comparisons of interest were paroxetine versus placebo in the intent-to-treat (ITT) population from the last-observation-carried-forward dataset, in which the last available postbaseline data from patients discontinuing the study are carried forward to all successive timepoints. The ITT population consisted of all patients who were randomly assigned to double-blind medication and who had at least 1 postbaseline efficacy assessment. The protocol-defined study endpoint was week 12.

Continuous efficacy variables (i.e., all measures except response and remission) were analyzed by analysis of variance using the general linear models procedure in Statistical Analysis System SAS version 6.12. The proportions of patients in the treatment groups achieving response (CGI-I score of 1 or 2) and remission (total CAPS-2 score < 20) were investigated by logistic regression (PROC GENMOD in SAS), for which the results are presented in terms of odds ratios (i.e., the odds of the response with paroxetine relative to the odds of response with placebo). Included in the statistical models were treatment group, center, and the following covariates: baseline score, gender, trauma type, time since trauma, and baseline MADRS

Table 1. Demographic and Baseline Clinical Characteristics of Randomized Patients, Intent-to-Treat Population

Characteristic	Placebo (N = 156)	Paroxetine (N = 151)
Age, y, mean (range)	39.8 (18–78)	41.9 (19–69)
Time since index trauma, y, mean (SD)	15.5 (14.8)	14.2 (12.3)
Gender distribution, %		
Male	34.6	33.8
Female	65.4	66.2
Race, %		
African American	7.7	11.3
Asian	1.3	1.3
White	75.6	68.9
Other	15.4	18.5

score. Treatment-by-covariate interactions were assessed at the 10% significance level. All other statistical tests were performed at the 5% significance level, with 95% confidence intervals (CIs) constructed around the differences between paroxetine and placebo. A post hoc analysis was performed to compare the proportions of patients in each treatment group achieving remission. A second post hoc analysis was conducted to address the question of whether paroxetine was effective on the primary efficacy measures in men and women.

RESULTS

Patients

A total of 323 patients were randomly assigned to double-blind study medication; 12 paroxetine patients and 4 placebo patients were lost to follow-up after the baseline visit. The demographic and mean baseline clinical characteristics of the 307 patients who comprised the ITT population are presented in Table 1. The treatment groups were comparable with respect to the distribution of gender and race and were also very similar with regard to the time since index trauma and baseline clinical measures. The distribution of trauma types was also comparable between the groups, with the most common trauma types being physical or sexual assault (50.6% in the placebo group vs. 47.7% in the paroxetine group), seeing someone hurt or die (18.6% vs. 19.2%), serious accident or injury (7.7% vs. 13.2%), and exposure to combat (7.1% vs. 6.6%). Current major depressive disorder was recorded for 33.3% of the placebo group and 37.1% of the paroxetine group. Similar proportions of patients in the 2 treatment groups presented with the following comorbid anxiety disorders: generalized anxiety disorder (15.4% in the placebo group vs. 16.6% in the paroxetine group), panic disorder (11.5% vs. 9.9%), social anxiety disorder (10.3% vs. 7.3%), and OCD (2.6% vs. 2.0%).

The mean ± SD dosage of paroxetine during the study was 27.6 ± 6.72 mg/day. In those patients completing the 12-week treatment period, paroxetine dosages were fairly evenly distributed among the 4 dosage levels: 22% of patients were taking 20 mg/day, 24% were taking 30 mg/day, 28% were taking 40 mg/day, and 25% were taking 50 mg/day.

Efficacy

Table 2 presents the baseline total score, the change from baseline, and the covariate-adjusted treatment differences for the CAPS-2 and the secondary efficacy measures for the 2 treatment groups. For all measures, improvement was statistically significantly greater in the paroxetine group than in the placebo group. Analysis of the data from the assessment timepoints shows that paroxetine effects on the CAPS-2 were significantly greater than those of placebo at weeks 4, 8, and 12 (Figure 1A), with the greatest portion of improvement occurring by week 8. Moreover, paroxetine treatment led to significantly greater improvement than placebo in each of the 3 PTSD symptom clusters. This was demonstrated both on the CAPS-2 and DTS cluster scores at the study endpoint (Table 2; also see Figure 1A). Significantly greater improvement in the paroxetine-treated patients was observed as early as week 4 for the hyperarousal symptom cluster of the CAPS-2 and at week 8 for avoidance/numbing symptoms (Figure 1B–D).

Reduction in the severity of depressive symptoms as measured by the MADRS was also significantly greater in the paroxetine group (see Table 2). There was no evidence from the covariate analysis that the treatment effect on the CAPS-2 total score varied by the severity of baseline depressive symptoms. There was, however, a statistically significant treatment-by-time-since-trauma interaction ($p = .037$ at study endpoint). Relative to other patients in the study sample, patients whose index trauma was more than 5 years prior to study start exhibited greater improvement in symptoms with paroxetine. This differential treatment effect may be explained in part by the fact that in the subgroup whose index trauma was less than 5 years before the study, there was a higher proportion of paroxetine-treated patients discontinuing study treatment (51.9%) compared with subgroups whose index trauma was 5 to 19 years (33.3%) and 20 years or more (27.3%) before study start.

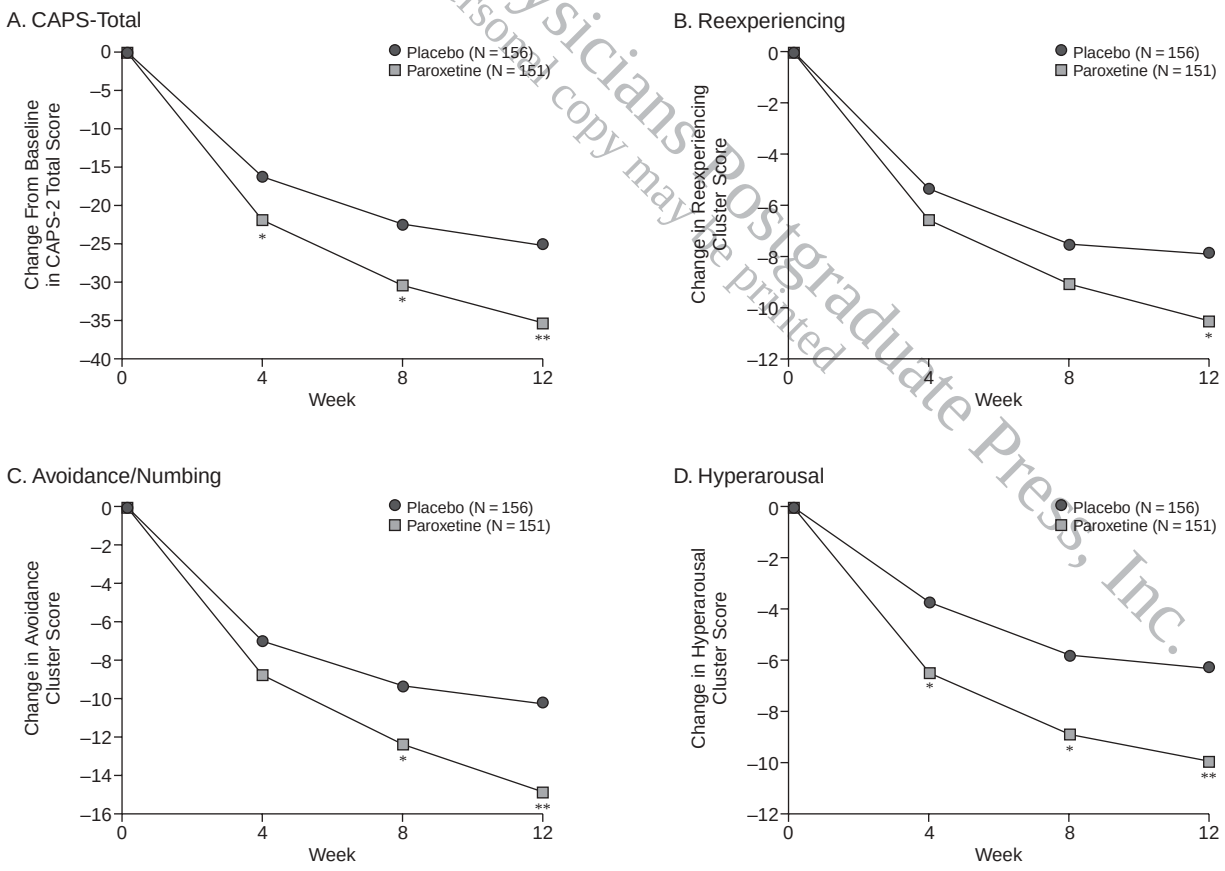
Compared with the odds for patients in the placebo group, the odds of achieving treatment response according to the CGI-I were significantly greater in the paroxetine group at all assessment timepoints from week 2 to the 12-week study endpoint (Table 3). For this variable, there was a significant treatment-by-trauma-type interaction ($p = .019$), with the proportion of responders being substantially greater in the trauma-type category "seeing someone hurt or die" than in the other categories. However, the proportion of responders was greater in the paroxetine group than in the placebo group for all categories. A significantly greater proportion of paroxetine-treated patients

Table 2. Efficacy of Paroxetine in the Treatment of Outpatients With Posttraumatic Stress Disorder (PTSD) at Study Endpoint[a]

	Placebo N = 156				Paroxetine N = 151				Adjusted Mean Differences, Paroxetine vs Placebo[b]	
	Baseline		Change		Baseline		Change			
Variable	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Difference (95% CI)	p Value
CAPS-2										
Total score	73.2	1.3	–24.7	2.0	74.3	1.4	–35.5	2.0	–10.6 (–16.2 to –5.0)	< .001
Cluster scores										
Reexperiencing	20.7	0.5	–7.9	0.8	20.6	0.6	–10.5	0.7	–2.7 (–4.6 to –0.8)	.007
Avoidance	30.1	0.7	–10.4	1.0	30.4	0.7	–15.0	1.0	–4.8 (–7.4 to –2.2)	< .001
Hyperarousal	22.5	0.5	–6.3	0.7	23.3	0.5	–10.0	0.7	–3.4 (–5.3 to –1.4)	< .001
TOP-8 total score	18.2	4.6	–6.3	0.7	18.3	0.4	–9.3	0.7	–3.8 (–5.6 to –1.9)	< .001
DTS										
Total score	73.6	1.8	–23.3	2.3	73.1	1.9	–35.6	2.3	–12.6 (–18.8 to –6.4)	< .001
Cluster scores										
Intrusion	20.5	0.6	–7.9	0.8	20.0	0.7	–10.2	0.8	–2.7 (–4.6 to –0.7)	.009
Avoidance/numbing	29.6	0.9	–8.9	1.1	29.7	0.9	–15.0	1.0	–6.2 (–9.0 to –3.4)	< .001
Hyperarousal	23.5	0.6	–6.5	0.8	23.4	0.6	–10.4	0.8	–4.0 (–6.1 to –1.9)	< .001
SDS total score	17.3	0.6	–4.6	0.6	17.0	0.6	–7.2	0.7	–2.6 (–4.4 to –0.7)	.007
MADRS total score	21.2	0.7	–5.1	1.0	22.2	0.7	–9.6	1.1	–3.8 (–6.4 to –1.2)	.004

[a]Abbreviations: CAPS-2 = Clinician Administered PTSD Scale, CI = confidence interval, DTS = Davidson Trauma Scale, MADRS = Montgomery-Asberg Depression Rating Scale, SDS = Sheehan Disability Scale, TOP-8 = Treatment Outcome PTSD Scale.
[b]Least square means adjusted for treatment, center, gender, trauma type, time since trauma, and baseline PTSD and depressive symptoms.

Figure 1. Change From Baseline in the Clinician Administered PTSD Scale (CAPS-2) (A) Total, (B) Reexperiencing, (C) Avoidance/Numbing, and (D) Hyperarousal Scores[a]



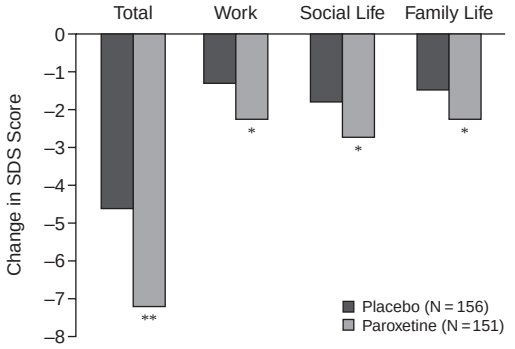
[a]Abbreviation: PTSD = posttraumatic stress disorder. Scores presented as adjusted least square means. Asterisks represent pairwise comparisons, paroxetine vs. placebo.
*p < .05.
**p < .001.

Table 3. Proportion of PTSD Patients Achieving Response[a]

Assessment Timepoint	Percentage of Patients: Placebo (N = 156)	Percentage of Patients: Paroxetine (N = 151)	Paroxetine vs Placebo: Odds Ratio[b]	95% CI	p Value
Week 1	5.0	7.0	1.9	0.7 to 5.4	.231
Week 2	5.3	22.3	5.4	2.4 to 12.3	< .001
Week 4	16.7	34.5	2.7	1.5 to 4.7	< .001
Week 6	27.3	48.6	2.9	1.7 to 4.9	< .001
Week 8	36.0	52.0	2.1	1.3 to 3.4	.003
Week 12	38.0	58.8	2.6	1.6 to 4.3	< .001

[a]Abbreviation: CI = confidence interval. Response defined as a score of 1 (very much improved) or 2 (much improved) on the Clinical Global Impressions-Global Improvement scale.
[b]The odds ratio represents the odds of improving with active treatment relative to that with placebo. Adjusted for center, gender, trauma type, time since trauma, and baseline Montgomery-Asberg Depression Rating Scale score.

Figure 2. Effect of Treatment on Functional Impairment: Change From Baseline in Sheehan Disability Scale (SDS) Total and Domain Scores[a]



[a]Presented as adjusted least square means. Negative change in score reflects clinical improvement. Asterisks represent pairwise comparisons, paroxetine vs. placebo.
*p < .05.
**p < .01.

achieved remission (CAPS-2 total score < 20) at study endpoint compared with placebo patients (29.4% vs. 16.5%; odds ratio = 2.29, 95% CI = 1.24 to 4.23; p = .008).

Functional improvement as assessed by the SDS was statistically greater at study endpoint for paroxetine-treated compared with placebo-treated patients (see Table 2). As shown in Figure 2, the improvement in the overall score reflects the changes in the 3 component domains of the SDS—work, social life, and family life—all of which were significantly greater in the paroxetine group.

Male and female patients treated with paroxetine achieved similar improvement in symptoms as measured by the CAPS-2 at the study endpoint, and this improvement was significantly greater than that obtained by placebo-treated patients (for men, difference for paroxetine vs. placebo: –15.15, 95% CI = –24.31 to –5.98, p = .002; for women, difference: –10.99, 95% CI = –18.68 to –3.30, p = .005). Equal proportions (58.8%) of male and female patients in the paroxetine group were rated as responders according to the CGI-I, with the odds of being a responder on paroxetine treatment compared with placebo being 2.47 and 2.76, respectively (men: 95% CI = 1.08 to 5.67, p = .03; women: 95% CI = 1.51 to 5.03, p < .001).

Tolerability and Safety

Similar proportions of patients from both groups completed 12 weeks of treatment (60.3% of placebo patients [94/156] and 61.6% of paroxetine patients [93/151]). The most frequently reported reason for study discontinuation was lost to follow-up among placebo-treated (10.9%) and adverse events among paroxetine-treated patients (11.9%), followed by noncompliance with the protocol in both groups (10.3% and 10.6%, respectively). Ten patients (6.4%) in the placebo group dropped out of the study due to adverse events.

No clinically relevant effects on laboratory parameters or vital signs were observed for paroxetine- or placebo-treated patients. Paroxetine was generally well-tolerated by patients in this study. The most commonly reported treatment-emergent adverse events in the paroxetine treatment group (incidence of at least 10% and twice that of placebo) were nausea (19.2% in the paroxetine group vs. 8.3% in the placebo group), somnolence (17.2% vs. 3.8%), dry mouth (13.9% vs. 4.5%), asthenia (13.2% vs. 5.8%), and abnormal ejaculation (11.8% vs. 3.7%). The incidence of non–ejaculation-related sexual adverse events (decreased libido, impotence, female genital disorders) was 7.3% in the paroxetine group and 2.6% in the placebo group. The majority of adverse events, regardless of treatment group, were rated as mild or moderate. Most adverse events occurred during the initial days of treatment and diminished with continued treatment.

DISCUSSION

The results of this placebo-controlled multicenter trial demonstrate that paroxetine, 20 to 50 mg daily, is an effective and well-tolerated treatment for chronic PTSD. Reductions in the scores of the CAPS-2, DTS, and TOP-8 in the paroxetine group—reductions that were significantly greater than those in the placebo group—indicate substantial alleviation of PTSD symptoms. The odds of achieving response were significantly greater in the paroxetine than in the placebo group from week 2, with approximately 60% of patients in the paroxetine group achieving response by the 12-week study endpoint, compared with 40% of the placebo patients (see Table 3). Nearly 30% of the paroxetine-treated patients compared with less than 20% of placebo patients achieved remission as defined by a CAPS-2 total score of less than 20. These results support the findings of a recently completed placebo-controlled, fixed-dosage study comparing 20 and 40 mg daily of paroxetine with placebo in the treatment of

chronic PTSD, in which both dosages were significantly more effective than placebo at weeks 4, 8, and 12.[42]

This study also demonstrated that the SSRI paroxetine effectively ameliorates each of the major symptom clusters of PTSD (reexperiencing, avoidance/numbing, and hyperarousal), as evaluated by both clinician raters (CAPS-2) and patient self-ratings (DTS). Statistically significant benefit in each of the symptom clusters was evident at week 4 and continued through week 12. Previous trials with fluoxetine[21] and sertraline[25,26] found that, using the CAPS as a primary efficacy measure, these SSRIs were effective in treating avoidance and hyperarousal symptoms of PTSD, but not reexperiencing symptoms. Intrusive (and hyperarousal) symptoms of PTSD are presently thought to derive from increased noradrenergic output from the locus ceruleus to the amygdala and hippocampus following acute stress and trauma.[43] Paroxetine, but not the SSRI citalopram, has been shown in preclinical studies to modulate noradrenergic output from the locus ceruleus, a differential effect that may result from the combination of paroxetine's strong serotonergic and weak but measurable anticholinergic activity.[44]

On average, the patients in this study exhibited severe PTSD symptomatology (baseline CAPS > 70; see Table 1). It is therefore noteworthy that the significant effects of paroxetine on patients' status as reflected by changes in the CAPS total score were observed after only a few weeks. This finding may be due, at least in part, to the demonstrated antianxiety properties of this medication. Recent reports by Pollack et al.[33] and Bellew et al.[45] concerning the treatment of generalized anxiety disorder with paroxetine show that reduction of psychic anxiety and tension, symptoms inherent in the PTSD hyperarousal symptom cluster, are alleviated early in treatment. This interpretation is supported by the finding from this study that significantly greater reduction in hyperarousal symptoms in the paroxetine treatment group compared with the placebo group occurred as early as week 4 (see Figure 1D).

The symptomatology and frequently chronic course of PTSD lead to substantial impairment of an individual's ability to function in interpersonal relationships at home and at work. The degree of impairment is reflected in the average baseline score of 17 on the SDS, which is greater than that observed in studies of panic disorder[39] and GAD[33,45] and comparable to pretreatment scores observed for social anxiety disorder.[30,39] Given the fact that the average time elapsed since the index trauma was around 15 years and many patients therefore had long-standing PTSD, it is remarkable that the paroxetine group showed significantly greater improvement in all 3 functional domains of the SDS that was significantly greater than with the placebo group after only 12 weeks of treatment. For PTSD patients otherwise haunted by intrusive reexperiencing symptoms and driven to social isolation by their avoidance of situations even vaguely reminiscent of the traumatic event, the degree of symptomatic and functional improvement offered by effective treatment could be a decisive step toward restoration of mental and physical well-being.

In this study, the clinically relevant question of whether medication response is different in men and women with PTSD was also addressed. In previous studies, this issue either was not formally addressed[26,27] or could not be adequately examined due to small sample size and/or differences in types of trauma between men and women.[22,46] The results of the present study clearly indicate that paroxetine is effective in treating men and women with PTSD.

Outcome on the primary efficacy variables did not vary according to patients' gender or the severity of PTSD and depressive symptoms at baseline. The covariate analysis did show at the week 12 endpoint a statistically significant treatment-by-time-since-trauma interaction on the CAPS-2 and a treatment-by-trauma-type interaction on the CGI-I. The first interaction may be related to the fact that more than half of the paroxetine-treated patients whose index trauma was less than 5 years prior to the study start withdrew early from the study. The most frequent reason (19%) for dropout in this subgroup was "lost to follow-up," which occurred much less frequently in the subgroups of patients whose index trauma was 5 to 19 years (1.9%) and 20 years or greater (9.1%) prior to the start of the study. It is possible that patients' ability to tolerate drug treatment or the time required for response to treatment may be influenced by the temporal proximity of the trauma, and this question certainly warrants further investigation. Regarding the second interaction, future research should also explore the possibility that the cascade of neurophysiologic responses to trauma may be affected by the type of trauma and/or the predisposing characteristics of the individual. For example, it is possible that PTSD resulting from direct personal trauma, especially violent trauma, may require a longer treatment period and/or higher medication dosages to attain response. However, it should be emphasized that all of the results presented here are adjusted for covariates and demonstrate a substantial benefit of paroxetine over placebo regardless of time since index trauma or trauma type.

Paroxetine was safe and well tolerated during this study. The dropout rate due to adverse events and the safety profile observed in the sample of PTSD patients is comparable to that reported for paroxetine in the treatment of other anxiety disorders.[29,32] The overall dropout rate was almost 40% in both treatment groups, which is higher than the rates of 30% to 35% reported in the brofaromine and sertraline studies and in the paroxetine fixed-dosage study.[17,26,27,42] A comparison of the dropout rates by cause between the previous SSRI studies[25,26,41] and the present study shows that the frequency of study discontinuation because of noncompliance with the protocol

was much greater in this study (approximately 11% versus 1%–4%). We can offer no plausible explanation for this finding, particularly in light of the fact that the paroxetine study reported by Marshall et al.[42] had identical inclusion and exclusion criteria and was conducted at the same time in similar clinical settings.

In this study, the mean dosage of paroxetine was 27.6 mg/day. In a fixed-dose, placebo-controlled study[42] comparing 20 and 40 mg/day of paroxetine in the treatment of PTSD, the improvement in symptoms as measured by the change from baseline in the CAPS-2 score and the proportion of CGI-I responders was not dose dependent, suggesting that paroxetine at 20 mg/day may be an effective dosage for most patients. Taken together, the results of these 2 studies indicate that physicians treating PTSD do not need to rapidly push the paroxetine dose to higher levels. However, the fact that the majority of patients completing 12 weeks of treatment were taking more than 30 mg/day of paroxetine may mean that higher doses of paroxetine may be necessary to reach maximal therapeutic effect.

The reduction of the mean baseline scores of the primary and secondary efficacy variables by 40% to 50% can certainly be considered clinically relevant, but in this study, as in other clinical trials of a single treatment of chronic PTSD,[25,26,42] a substantial proportion of patients did not achieve response. It is very well possible that, due to the chronic and debilitating nature of PTSD, patients showing little or only partial response over 12 weeks may have profited from a longer course of treatment with paroxetine. A recently published open-label study[47] indicates that extending treatment of PTSD with sertraline to 6 months does indeed enhance response, particularly in patients with severe baseline illness.[46] Further studies are therefore required to establish the long-term benefit and optimal duration of treatment of PTSD with paroxetine. This is an important question, given the epidemiologic evidence that many PTSD patients do not achieve remission after years of illness.[2] Moreover, investigations of the specific response of different types of trauma to pharmacotherapy could help to elucidate the pathophysiology of PTSD. Future research projects must also investigate under controlled conditions the combination of pharmacotherapy with psychotherapeutic approaches as a strategy to optimize treatment outcome.

Drug names: alprazolam (Xanax and others), amitriptyline (Elavil and others), citalopram (Celexa), clonazepam (Klonopin and others), fluoxetine (Prozac and others), lamotrigine (Lamictal), paroxetine (Paxil), phenelzine (Nardil), sertraline (Zoloft).

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