Fluoxetine Versus Placebo in Posttraumatic Stress Disorder

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Background: This study was designed to address the efficacy and tolerability of fluoxetine in patients with posttraumatic stress disorder (PTSD) as diagnosed using the Structured Clinical Interview for DSM-IV Axis I Disorders and the Clinician-Administered PTSD Scale (CAPS). The patient population included both civilians and combat veterans.

Method: This was a double-blind, randomized, placebo-controlled study conducted in Europe, Israel, and South Africa, primarily in war-torn countries. Patients were predominantly male (81%) and white (91%), with 48% exposed to a combat-related traumatic episode. Patients were randomly assigned to 12 weeks of acute treatment with fluoxetine, 20 to 80 mg/day (N = 226), or placebo (N = 75). The primary efficacy measurement was the mean change from baseline in the Treatment Outcome PTSD rating scale (TOP-8) total score, which was analyzed using a repeated-measures analysis of variance. Secondary assessments included the CAPS, the Davidson Trauma Scale, the Clinical Global Impressions-Severity of Illness scale (CGI-S), the CGI-Improvement scale (CGI-I), the Montgomery-Asberg Depression Rating Scale (MADRS), the Hamilton Rating Scale for Anxiety (HAM-A), and the Hopkins 90-Item Symptom Checklist-Revised.

Results: Fluoxetine was associated with a greater improvement from baseline in total TOP-8 score than was placebo. This difference was statistically significant by week 6 of treatment ($p < .001$) through the end of the acute phase of the study (week 12; $p = .006$). Compared with placebo, fluoxetine was also associated with significantly greater improvement in CAPS total score as well as intrusive and hyperarousal subscores and in CGI-S, CGI-I, HAM-A, and MADRS scores ($p < .05$). The presence of dissociative symptoms at baseline appeared to be a predictor of high placebo response. The mean fluoxetine dose at endpoint was 57 mg. There were no clinically significant safety differences.

Conclusion: Fluoxetine is effective and well tolerated in the treatment of PTSD. Most PTSD patients will respond satisfactorily at doses in the upper normal range for the usual antidepressant doses of fluoxetine.

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Posttraumatic stress disorder (PTSD), a syndrome characterized by psychopathologic responses to a traumatic event, has been recognized in the *Diagnostic and Statistical Manual of Mental Disorders* as a distinct diagnostic entity since 1980. PTSD is characterized by 3 specific groups of symptoms: intrusive behaviors (including recurrent and distressing recollections and dreams, recurrent illusions or flashback episodes, and intense physiologic distress), avoidance behaviors (including persistent avoidance of reminders of the trauma, psychological amnesia, and numbing of responsiveness), and hyperarousal (including insomnia, difficulties with concentration, and exaggerated startle response).

The lifetime prevalence of PTSD in the general population is between 1% and 9%,[1–3] with an even higher prevalence among particular subpopulations. An epidemiologic survey showed that the lifetime prevalence of PTSD is 3.5% in civilians exposed to physical attack and 20% in veterans wounded in Vietnam.[4] Another study indicated that the current incidence of PTSD is 15% among all Vietnam veterans, 21% among African American Vietnam veterans, and 28% among Hispanic Vietnam veterans.[5] Patients suffering from PTSD also commonly suffer from other comorbid psychiatric disorders. The prevalence of major depression is 10 to 15 times higher among veterans with PTSD than among patients without PTSD, and the prevalence of anxiety disorders is 20 times higher.[5] Other common comorbidities include dysthymia, sexual dysfunction, obsessive-compulsive disorder (OCD), social phobia, and agoraphobia.[6] Survival analysis shows that more than one third of people with an initial episode of PTSD fail to recover even after many years.[7]

It appears that PTSD may be at least partially responsive to pharmacotherapy. Treatment goals in the pharmacologic management of PTSD include reduction of intrusive thoughts, reduction of avoidance behavior, improvement of hyperarousal symptoms, and improvement

of depressive symptoms. Both tricyclic antidepressants and phenelzine, a monoamine oxidase inhibitor, have demonstrated efficacy in double-blind controlled clinical trials, although no treatment has been effective on all components of the symptom picture.[8–13]

The selective serotonin reuptake inhibitors (SSRIs), with fewer and less troublesome side effects, have also been evaluated in the treatment of PTSD. Significant superiority of sertraline compared with placebo was observed in a 12-week trial of 187 outpatients with PTSD. Patients were predominantly female (73%), with 61.5% experiencing physical or sexual assault. Treatment with sertraline yielded significantly greater improvement than placebo in the Clinician-Administered PTSD Scale-2 (CAPS-2) total score, avoidance/numbing subscore, and hyperarousal subscore, but failed to show superiority in the reexperiencing/intrusion subscore. Response rates (defined as a 30% or greater decrease in CAPS-2 total score and a Clinical Global Impressions-Improvement scale [CGI-I] score of 1 or 2) were 53% in the sertraline group and 32% in the placebo group.[14]

A post hoc gender analysis[15] was conducted using data from this study and 2 other large, 12-week placebo-controlled studies of sertraline and placebo in civilian populations with PTSD. Two[14,16] of the 3 studies demonstrated sertraline to be efficacious in the overall study population, with strong evidence of efficacy in women. However, efficacy in men was not demonstrated on any of the primary efficacy measurements.[15]

Fluoxetine has also been studied in the treatment of PTSD and was found to be effective in 2 open-label studies[17,18] and in 2 double-blind, placebo-controlled studies.[19,20] Most of these studies were conducted in either female patients or in combat veterans with chronic PTSD. In the study by Connor et al.,[20] the patient population was predominantly female (91%), with most exposed to traumas such as rape, incest, spousal sexual abuse, traumatic bereavement, or violent crime. In the study by McDougle et al.,[17] all patients were Vietnam veterans who had experienced symptoms of PTSD for more than 10 years. Similarly, in the study by Nagy et al.,[18] all patients were male combat veterans who had served in either Vietnam, Korea, or World War II, many with disabling symptoms that had persisted for 20 years. The study by van der Kolk et al.,[19] which was conducted in both civilian patients in a trauma clinic and combat veterans in a Veterans Administration (VA) hospital, was of particular interest because it showed that fluoxetine was associated with significantly faster and greater improvements in the civilian population relative to the veteran population. However, the veteran population, as a group, had more severe PTSD symptoms upon entering the study and had been receiving some form of therapy for more than a decade.

A lack of efficacy for fluoxetine among male veterans with severe, chronic PTSD was also seen in a small study by Hertzberg et al.,[21] who evaluated fluoxetine and placebo in a 12-week double-blind study. One (17%) of 6 fluoxetine patients and 2 (33%) of 6 placebo patients demonstrated a response. The mean fluoxetine dose at endpoint was 48 mg/day, with a range of 10 to 60 mg/day.

The finding by van der Kolk et al.[19] that civilian patients who are just beginning to seek treatment for their past trauma are more responsive to fluoxetine treatment than combat veterans with a greater length of prior treatment suggests that fluoxetine might show the same robust response in a population of combat patients without chronic symptoms. The present double-blind, placebo-controlled study, conducted in Belgium, Bosnia, Croatia, Israel, South Africa, and Yugoslavia, was designed to address this possibility and to expand on earlier observations. Patients were predominantly male, relatively young, and had experienced quite recent traumas.

METHOD

Patient Population

Participants in the trial were men and women aged 18 to 65 years who met DSM-IV criteria for PTSD according to the Structured Clinical Interview for DSM-IV Axis I Disorders, Investigator Version (SCID-I [modified])[22] and the CAPS, Current Diagnostic Version (CAPS-DX).[23] To enroll, patients must have had a total score ≥ 50 on the CAPS-DX and a score ≥ 4 on the Clinical Global Impressions-Severity of Illness scale (CGI-S) at baseline (Visit 2). Patients with a Montgomery-Asberg Depression Rating Scale (MADRS) score > 20 at baseline were ineligible for the study. Exclusion criteria included a serious comorbid illness, serious suicidal risk or hetero-aggressivity, or a diagnosis of an Axis I psychiatric disorder as defined by DSM-IV criteria within the 5 years prior to the primary traumatic episode. Patients diagnosed with bipolar disorder, OCD, or schizophrenia at any time were excluded. Patients with a diagnosis of any Axis I psychiatric disorder or comorbidity following the primary traumatic episode, with the exception of generalized anxiety disorder, depression, panic disorder, or social phobia, were excluded. Patients with substance abuse following the traumatic episode were allowed to enroll, provided the abuse had resolved at least 6 months prior to study entry.

The study was conducted at 18 study centers in Belgium, Bosnia, Croatia, Israel, South Africa, and Yugoslavia. The institutional review board for each site reviewed the study, and written informed consent was obtained from all participants.

Study Design

After a 1- to 2-week diagnostic evaluation period during which no study drug was given, patients were randomly assigned under double-blind conditions to 12

weeks of acute treatment with fluoxetine or placebo. Fluoxetine-treated patients initially received a dosage of 20 mg/day. This dose could have been increased in 20-mg increments at each of 3 titration points based on predefined response criteria to a maximum dosage of 80 mg/day.

Patients were seen at 3-week intervals throughout the 12-week acute treatment period. The study also included a 24-week relapse prevention period for patients who responded to acute treatment; however, the results of this phase will be discussed elsewhere.

A computer-generated randomization sequence was used to determine each patient's treatment group assignment. Emergency codes, generated by a computer drug-labeling system, were available to the investigator. These codes, which revealed the patient's treatment group, were opened during the study only if the choice of follow-up treatment depended on the patient's treatment assignment.

Outcome Measures

The primary measure of improvement in PTSD symptoms was the mean change from baseline in the Treatment Outcome PTSD scale (TOP-8)[24] total score. Secondary assessments included the CAPS total, intrusive, avoidance, and hyperarousal scores; the CGI-S[25]; the CGI-I[25]; and the Davidson Trauma Scale (DTS)[26] total, intrusive, avoidance, and hyperarousal scores. Improvement in comorbid psychiatric disorders was measured using the MADRS,[27] the Hamilton Rating Scale for Anxiety (HAM-A),[28] and the Hopkins 90-Item Symptom Checklist-Revised (SCL-90-R).[29,30] Dissociative symptoms at baseline were assessed using the Dissociative Experiences Scale (DES),[31] an 8-item self-rated instrument in which the patient assesses the frequency of dissociative experiences on a scale from 1 to 10.

The 2 patient-rated scales, the DTS and SCL-90-R, were translated into the appropriate language. The actual case report form pages that the patients completed were written in the appropriate language (French, Serbo-Croatian, Bosnian, Hebrew, or English), and the carbon copy under the native language was written in English.

Safety was assessed by the evaluation of treatment-emergent adverse events, discontinuations for adverse events, vital signs measurements, and clinical laboratory tests. Adverse events were elicited by nonprobing inquiry and were recorded regardless of perceived causality. An event was considered treatment emergent if it occurred for the first time or worsened during the double-blind treatment period. Investigators assessed patient compliance at each visit by direct questioning and by counting returned medication capsules. A patient was considered noncompliant if he or she missed more than 4 consecutive days or more than 10 cumulative days of study medication. A patient was also considered noncompliant if the ratio of the number of capsules taken to the number of capsules prescribed was not between 0.8 and 1.2 inclusive.

Statistical Methods

Analyses of change from baseline in TOP-8, DTS, CGI-S, MADRS, HAM-A, and SCL-90-R scores were conducted using a repeated-measures analysis of variance (ANOVA) model with visit, treatment, investigator, and visit-by-treatment interaction as effects in the model and with the corresponding baseline score included as a covariate. An unstructured covariance matrix was fit to the within-patient repeated measures. Change from baseline to each visit was tested between treatment groups using contrasts within the repeated-measures model. The analysis of CGI-I scores was done in a similar manner using raw postbaseline values. The model for CGI-I scores did not include corresponding baseline score, since baseline is not collected for this measure. For the CAPS total scores and subscores, which were collected only at baseline and endpoint, analyses of the change from baseline to endpoint (last observation carried forward [LOCF]) were conducted using analysis of variance with treatment and investigator as effects in the model.

Response rates were also used to compare efficacy between fluoxetine- and placebo-treated patients. Response was defined as a 50% or greater reduction in the TOP-8 total score from baseline and a CGI-S score of 1 or 2. Only patients with at least one postbaseline value were included in the analysis. The Fisher exact test was used to compare treatment differences.

Changes from baseline in the TOP-8 total score were also analyzed for differences across subgroups and within subgroups. Subgroups were based on gender, age (< 45 or ≥ 45 years), type of trauma (combat-related or non–combat-related), number of traumas (1 or ≥ 2), and presence of dissociative symptoms at baseline (DES total score = 0 or DES total score > 0). Across subgroups, repeated-measures analyses were conducted with visit, treatment, investigator, visit-by-treatment interaction, subgroup, treatment-by-subgroup interaction, and the corresponding baseline score included as terms in the model. Within subgroups, repeated-measures analyses were conducted with visit, treatment, investigator, visit-by-treatment interaction, and the corresponding baseline score included as terms in the model. Effect sizes were calculated by obtaining the difference between treatment groups in the least square means divided by the estimated standard deviation obtained from the repeated-measures ANOVA model.

The combat-related subgroups were determined based on a traumatic events checklist completed at baseline. Patients were instructed to select all applicable events. Patients who specified "combat-related" (implying that the patient was an active participant in military action and experienced the traumatic event during combat) were

Table 1. Baseline Clinical Characteristics and Illness Severity[a]

Demographic	Fluoxetine N = 226	Placebo N = 75	p Value
Gender, % male	80	85	.392
Age, y	38.2 (9.5)	37.1 (8.8)	.371
Origin, % white	89	95	.786
Traumatic event(s) reported, %			
Combat-related	49	45	.689
Victim of war or witness of war event	48	44	.595
Witness of another person's death	33	28	.475
Number of traumas, %			
1	53	55	
≥ 2	47	45	.894
TOP-8 total score	19.5 (4.0)	19.1 (3.6)	.304
CAPS total score	80.5 (16.0)	81.3 (14.1)	.762
CAPS intrusive score	24.7 (5.8)	24.8 (5.3)	.944
CAPS avoidance score	31.4 (7.4)	31.9 (6.9)	.569
CAPS hyperarousal score	24.4 (5.8)	24.6 (4.9)	.872
DTS total score	75.6 (22.6)	76.2 (22.7)	.722
DTS instrusive score	23.5 (7.4)	23.6 (7.5)	.814
DTS avoidance score	28.1 (10.5)	28.6 (10.6)	.710
DTS hyperarousal score	24.0 (7.1)	23.8 (7.7)	.958
CGI-S score	4.8 (0.7)	5.0 (0.8)	.048
MADRS total score	16.5 (4.1)	16.9 (5.3)	.501
HAM-A total score	18.5 (6.3)	17.6 (5.7)	.197
SCL-90-R total score	154.6 (59.8)	152.1 (56.2)	.644
DES total score	7.2 (10.8)	6.3 (8.3)	.472

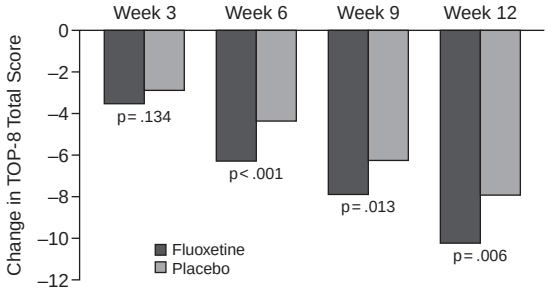
[a]All data are reported as mean (SD) unless otherwise indicated. Abbreviations: CAPS = Clinician-Administered PTSD Scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, DES = Dissociative Experiences Scale, DTS = Davidson Trauma Scale, HAM-A = Hamilton Rating Scale for Anxiety, MADRS = Montgomery-Asberg Depression Rating Scale, PTSD = posttraumatic stress disorder, SCL-90-R = Hopkins 90-Item Symptoms Checklist-Revised, TOP-8 = Treatment Outcome PTSD Scale. The Fisher exact test was used for all categorical variables, and type III sum of squares analysis of variance (SAS Procedure Linear General Model including treatment and investigator) was used for all continuous variables.

included in the combat-related subgroup. Patients who did not specify "combat-related" were included in the non–combat-related subgroup. The terms *victim of war or witness of catastrophic event of war*, *terrorist attack*, and *concentration camp experience* were not considered combat related unless the patient also selected the term *combat-related.*

Treatment differences in patient characteristics at baseline were assessed using the Fisher exact test for categorical variables and type III sums of squares ANOVA for continuous variables. The ANOVA model included investigator and treatment. Treatment-emergent adverse events and treatment-emergent abnormal laboratory values were analyzed using the Fisher exact test. The distribution of doses received by fluoxetine patients was summarized by visit.

All analyses were based upon the intent-to-treat principle and were performed using SAS software (SAS Institute Inc., Cary, N.C., 1991). Tests of treatment effects were conducted at a 2-sided alpha level of .05. Investigators with fewer than 2 randomized patients per treatment group were pooled for statistical analysis purposes.

Figure 1. Mean Change From Baseline in Treatment Outcome PTSD Scale (TOP-8) Total Score[a]



[a]Abbreviation: PTSD = posttraumatic stress disorder. Repeated-measures model with visit, treatment, investigator, and visit-by-treatment interaction as effects.

RESULTS

Sample Description

Of 330 patients who were screened for eligibility, 301 met entry criteria after the baseline evaluation period and were randomly assigned to either fluoxetine (N = 226) or placebo (N = 75). Patients were predominantly male (81%) and white (91%), with many exposed to multiple traumas of combat-related type (48%) and/or as a victim of war or witness of war event (47%). Demographic data and baseline clinical characteristics were similar for both groups, with the exception of a statistically significant difference in CGI-S score (Table 1).

Medication compliance was high for both groups (97%–100% at all timepoints for each group). There were no significant differences between treatment groups in compliance at any visit. The mean exposure to study drug was 80 days for fluoxetine-treated patients and 79 days for placebo-treated patients. The mean final dose was 57 mg.

Efficacy

In repeated-measures analyses of the change from baseline to week 12 in the TOP-8 total score, fluoxetine-treated patients experienced a significantly greater improvement in the TOP-8 total score compared with placebo-treated patients (fluoxetine, –10.3; placebo, –8.0; p = .006). There was an effect size of 0.40 in favor of fluoxetine. A further analysis of the change from baseline to each visit showed that the improvement was significant beginning at 6 weeks (Figure 1). Response rates (defined as a 50% or greater decrease in the TOP-8 total score and a CGI-S score of 1 or 2) were 59.9% in the fluoxetine-treated group and 43.8% in the placebo group (p = .020).

An LOCF analysis of the change from baseline to endpoint in the CAPS scores demonstrated that fluoxetine-treated patients experienced significantly greater improvement compared with placebo-treated patients on the CAPS total score (p = .021), the intrusive subscore

Table 2. Changes from Baseline in Secondary Assessments[a]

Outcome Measure	Fluoxetine	Placebo	p Value
CAPS total score[b]	–34.6 (28.1)	–26.8 (26.1)	.021
CAPS intrusive score[b]	–11.4 (9.6)	–8.4 (9.3)	.010
CAPS avoidance score[b]	–13.1 (11.7)	–10.6 (10.4)	.068
CAPS hyperarousal score[b]	–10.0 (8.7)	–7.7 (8.1)	.035
DTS total score[c]	–33.8 (2.25)	–27.3 (3.66)	.117
DTS instrusive score[c]	–10.5 (0.72)	–8.9 (1.21)	.237
DTS avoidance score[c]	–12.4 (0.92)	–9.4 (1.50)	.076
DTS hyperarousal score[c]	–9.8 (0.70)	–7.1 (1.18)	.041
CGI-S score[c]	–2.2 (0.10)	–1.8 (0.17)	.039
CGI-I score[d]	2.2 (0.10)	2.7 (0.16)	.003
MADRS score[c]	–6.5 (0.45)	–3.5 (0.75)	< .001
HAM-A score[c]	–8.7 (0.48)	–5.7 (0.79)	.001
SCL-90-R score[c]	–51.8 (4.40)	–36.4 (7.20)	.058

[a]Abbreviations: CAPS = Clinician-Administered PTSD Scale, DTS = Davidson Trauma Scale, CGI-I = Clinical Global Impressions-Improvement Scale, CGI-S = CGI-Severity of Illness scale, HAM-A = Hamilton Rating Scale for Anxiety, MADRS = Montgomery-Asberg Depression Rating Scale, PTSD = posttraumatic stress disorder, SCL-90-R = Hopkins 90-Item Symptoms Checklist-Revised.
[b]CAPS changes from baseline to endpoint were analyzed using a last observation carried forward model with treatment and investigator as effects. Data are reported as mean (SD).
[c]DTS, CGI-S, MADRS, HAM-A, and SCL-90-R changes from baseline to week 12 were analyzed using a repeated-measures model with visit, treatment, investigator, and visit-by-treatment interaction as effects and with the corresponding baseline score included as a covariate. Data are reported as least square mean (SE).
[d]CGI-I analysis was performed on postbaseline measures using a repeated-measures model with visit, treatment, investigator, and visit-by-treatment interaction as effects. Data are reported as least square mean (SE).

(p = .010), and the hyperarousal subscore (p = .035). The difference between the 2 treatment groups in the avoidance subscore approached significance (p = .068). In the repeated-measures analysis of other secondary assessments, fluoxetine-treated patients experienced significantly greater improvement compared with placebo-treated patients in CGI-S, CGI-I, HAM-A, and MADRS scores (Table 2).

Subgroup analyses of the TOP-8 total score were performed on the basis of gender, age, type of trauma (combat-related or non–combat-related), number of traumas (1 or ≥ 2), and presence of dissociative symptoms at baseline (DES total score = 0 or DES total score > 0). Significantly greater improvements compared with placebo treatment were associated with fluoxetine-treated patients who were male (p = .026), white (p = .005), or less than 45 years old (p = .034); those with combat-related trauma (p < .001); those who suffered more than 1 traumatic event (p < .001); and those with no dissociative symptoms (p < .001) (Table 3). Effect sizes were particularly robust among those with combat-related trauma (0.78) and those with no dissociative symptoms (1.20). Although the analyses did not show significantly greater improvement in female patients or patients ≥ 45 years old, the effect sizes for those subgroups were actually higher than in their corresponding comparison subgroup (men vs. women, 0.35 vs. 0.53; < 45 years vs. ≥ 45 years, 0.36 vs. 0.46). The placebo response rates were generally high, especially in the non–combat-related subgroup, the single traumatic event subgroup, and the dissociative symptoms subgroup (least square means for non–combat-related trauma: fluoxetine, –10.3; placebo, –9.6; single traumatic event: fluoxetine, –9.9; placebo, –9.7; dissociative symptoms: fluoxetine, –10.7; placebo, –9.8).

Safety

The percentage of patients reporting 1 or more treatment-emergent adverse events was similar for both treatment groups (fluoxetine, 53%; placebo, 55%). There were no statistically significant differences in the percentage of patients reporting any single event. The adverse events most commonly reported by fluoxetine-treated patients were headache (16%), nausea (14%), insomnia (12%), and dry mouth (7%); those most commonly reported by placebo-treated patients were headache (15%), insomnia (12%), anxiety (7%), nausea (7%), and dry mouth (7%). The percentage of discontinuations due to adverse events was similar for both groups (2.7% for fluoxetine, 4.0% for placebo; p = .695). There were no statistically significant differences between treatment groups in the number of discontinuations due to lack of efficacy (p = .181), entry criteria not met (p = .186), lost to follow-up (p = .119), patient decision (p = 1.000), or noncompliance (p = .374). No adverse event leading to discontinuation was reported by more than 1 patient in either treatment group. Only 2 patients, both of whom were in the placebo-treatment group, experienced serious adverse events.

There were no significant differences between the 2 groups in any vital sign measure. There was a statistically significant difference between the 2 treatment groups in only 1 laboratory analyte, the erythrocyte (red blood cell) count. The change from baseline for fluoxetine-treated patients was –0.087; for placebo-treated patients, 0.016 (p = .018).

DISCUSSION

The results of this study provide evidence that the majority of fluoxetine-treated patients with PTSD experience significant improvement in overall PTSD symptoms as well as reduction in symptomatology for comorbid disorders. Fluoxetine was associated with statistically greater improvement compared with placebo in clinician-rated measures, including TOP-8 total score, CAPS total score, CAPS intrusive subscore, CAPS hyperarousal subscore, CGI-S score, and CGI-I score. The total score of the patient-rated DTS failed to show significant differences in the improvement of PTSD symptomatology. However, the improvement in the hyperarousal subscore significantly favored fluoxetine treatment as compared with treatment with placebo.

Analyses of the MADRS total score, HAM-A total score, and SCL-90-R total score were used to evaluate the

Table 3. Subgroup Analysis of Treatment Outcome PTSD Scale (TOP-8) Total Score Changes from Baseline to Week 12[a]

Subgroup	Total N	Subgroup Term p Value	Treatment-by-Subgroup Interaction p Value	Treatment	N	Least Square Mean (SE)	Effect Size	Treatment p Value
Gender								
Male	245	.129	.586	Fluoxetine	181	–9.8 (0.49)	0.35	.026
				Placebo	64	–7.8 (0.77)		
Female	56			Fluoxetine	45	–10.8 (1.25)	0.53	.169
				Placebo	11	–6.9 (2.54)		
Age								
< 45	223	.994	.779	Fluoxetine	168	–10.7 (0.50)	0.36	.034
				Placebo	55	–8.7 (0.83)		
≥ 45	78			Fluoxetine	58	–8.9 (0.95)	0.46	.113
				Placebo	20	–6.1 (1.59)		
Origin								
White	273	< .001	.086	Fluoxetine	202	–9.8 (0.47)	0.42	.005
				Placebo	71	–7.4 (0.76)		
Nonwhite	28			Fluoxetine	24	–14.4 (1.09)	–1.0	.156
				Placebo	4	–18.2 (2.53)		
Combat related								
Yes	144	.172	.769	Fluoxetine	110	–9.4 (0.72)	0.78	< .001
				Placebo	34	–5.0 (1.10)		
No	157			Fluoxetine	116	–10.3 (0.65)	0.12	.543
				Placebo	41	–9.6 (1.05)		
No. of Traumas								
1	161	.098	.250	Fluoxetine	120	–9.9 (0.61)	0.04	.847
				Placebo	41	–9.7 (1.00)		
≥ 2	140			Fluoxetine	106	–9.9 (0.74)	0.72	< .001
				Placebo	34	–5.1 (1.16)		
Dissociative symptoms								
DES total score = 0	87	.692	.026	Fluoxetine	66	–9.9 (0.69)	1.20	< .001
				Placebo	21	–4.4 (1.17)		
DES total score > 0	214			Fluoxetine	160	–10.7 (0.55)	0.15	.383
				Placebo	54	–9.8 (0.89)		

[a]Abbreviations: DES = Dissociative Experiences Scale, PTSD = posttraumatic stress disorder. Data were analyzed using a repeated-measures model with visit, treatment, investigator, visit-by-treatment interaction, subgroup, and treatment-by-subgroup interaction as effects and with the corresponding baseline score included as a covariate. Within-subgroup analyses used a repeated-measures model with visit, treatment, investigator, and visit-by-treatment interaction as effects and with the corresponding baseline score included as a covariate.

change in patients' comorbid disorders. Compared with placebo-treated patients, fluoxetine-treated patients experienced significantly greater improvement in the MADRS total score and HAM-A total score, with a trend toward greater improvement in the SCL-90-R total score. Interestingly, both of the instruments that failed to show significant differences favoring fluoxetine treatment (DTS and SCL-90-R) are patient-rated scales.

Subgroup analyses of the TOP-8 total score showed significantly greater improvements compared with placebo treatment for fluoxetine-treated patients who were male, white, and less than 45 years old; those with combat-related trauma; those who suffered more than 1 traumatic event; and those with no dissociative symptoms. Although the analyses did not show significantly greater improvement in women or patients ≥ 45 years old, the sample sizes for those patient populations were small, and the similarity in effect sizes across subgroups indicates that there was a lack of statistical power for those comparisons. In addition, there were not significant improvements in the non–combat-related subgroup, the single traumatic event subgroup, or the dissociative symptoms subgroup, although this can be partially explained by the very high placebo response rate in these 3 subgroups.

In the subgroup analysis based on dissociative symptoms, the treatment-by-subgroup interaction was statistically significant (p = .026), indicating that the difference observed between the fluoxetine and placebo treatment groups differed between the patients with and without dissociative symptoms at baseline. This results in a striking difference in effect sizes between the 2 subgroups (1.2 for patients with dissociative symptoms, 0.15 for patients without dissociative symptoms). The improvement in TOP-8 total score for the fluoxetine-treated patients with dissociative symptoms (–10.7) was similar to the improvement for patients without dissociative symptoms (–9.9). However, the improvement in TOP-8 total score for the placebo-treated patients with dissociative symptoms (–9.8) was quite different from the improvement for patients without dissociative symptoms (–4.4). These findings suggest that dissociative symptoms at baseline may be a predictor of high placebo response. Several authors have suggested that the presence of significant

dissociative symptoms represents a biologically different subtype of PTSD, with a possible left hemisphere dysfunction.[32,33] The DSM-IV[34] criteria for PTSD include several references to dissociative symptoms in criterion B3 (dissociative states in which components of the event are relived and the person behaves as though experiencing the event at that moment) and criterion C3 (amnesia for an important aspect of the traumatic event). A study of 65 Vietnam veteran patients[35] found that patients with PTSD had significantly higher hypnotizability scores than other psychiatric groups, suggesting that spontaneous dissociation is an important component of PTSD symptoms.

The robust response in the combat-related trauma subgroup differs from the findings of van der Kolk et al.,[19] who found that non-VA patients responded much better to fluoxetine treatment than VA patients, and from the results of Hertzberg et al.,[21] who found that fluoxetine was ineffective in male combat veterans. In addition, the efficacy of fluoxetine in male patients differs from the findings of Friedman et al.,[15] who did not demonstrate efficacy in men on any of their primary efficacy measurements. However, in contrast to the earlier studies in which the majority of patients had severe PTSD symptoms upon entering the study and had been receiving some form of therapy for more than a decade, in this study patients were relatively young and had experienced quite recent traumas. These findings are important because they suggest that younger combat patients who are just beginning to confront the realities of their past trauma are more responsive to fluoxetine treatment than veterans with greater chronicity of symptoms.

The safety and tolerability of fluoxetine in this study were comparable to those observed in previous studies of fluoxetine in PTSD and in a large number of fluoxetine trials for other indications. Fluoxetine was generally well tolerated, with no statistically significant difference between treatment groups in the incidence of any individual adverse event, nor any difference in dropout rate due to adverse events. These data provide no evidence of unique or increased risks relative to those observed in other disorders in which fluoxetine has been studied.

In a study of predominately female patients with non–combat-related PTSD,[20] the median daily dose of fluoxetine was 30 mg. However, data from other studies[18,19,36] have suggested that patients with PTSD may require higher fluoxetine doses and/or duration than those typically used to obtain symptomatic relief in depressed patients. The findings of this study are supportive of this practice. The mean fluoxetine dose at endpoint was 57 mg, indicating that most patients required upward titration from their initial dosage of 20 mg/day. Improvement from baseline in total TOP-8 score was statistically significant beginning at week 6 of treatment. In contrast, results of fluoxetine depression studies generally support 20 mg/day as the optimal dose, with a statistically significant treatment separation from placebo as early as week 1.[37,38]

One limitation of the present study is the use of relatively new rating scales as primary and secondary measures of PTSD severity. A variety of rating instruments have been used in previous clinical studies, including the CAPS, TOP-8, DTS, Structured Interview for PTSD, and Duke Global Rating Scale. However, a single standard severity assessment tool for PTSD has not been adopted by the clinical community. For this study, the clinician-rated TOP-8 was selected as the primary efficacy measure because of its brief format, sensitivity to changes in symptomatology during pharmacotherapy, and ability to detect drug versus placebo differences.[24] The CAPS, which has been validated and shown to be highly reliable,[23] was also used as both a diagnostic tool and a secondary efficacy measure. The DTS, a patient-rated scale, was used in this study to provide additional correlation data against the clinician-rated instruments. The other efficacy measurements, quality-of-life measurements, and safety assessments are commonly used clinical assessments. These measurements have been documented and validated in the literature and are regarded as reliable, accurate, and relevant.

In summary, this study provides further evidence that fluoxetine is effective and well tolerated among patients with PTSD. Most patients will respond satisfactorily at doses in the upper normal range for the usual antidepressant doses. Although past literature has suggested that pharmacologic treatment is ineffective in combat veterans, this study provides evidence that men who have been exposed to combat trauma can show an excellent response to SSRI treatment.

Drug names: fluoxetine (Prozac and others), phenelzine (Nardil), sertraline (Zoloft).

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