0271-0749/93/1302-0107$03.00/0
Journal of Clinical Psychopharmacology
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Vol. 13, No. 2
Printed in U.S.A.

Open Prospective Trial of Fluoxetine for Posttraumatic Stress Disorder

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Twenty-seven patients with combat-related posttraumatic stress disorder (PTSD) entered an open, prospective, 10-week trial of fluoxetine, beginning with 20 mg/day and increasing to 80 mg/day until response was optimal or side effects prohibited dose increase. Nineteen patients completed 3 or more weeks and were included in the data analysis. Total Clinician-Administered PTSD Scale scores decreased from a mean of 64.5 at baseline to 42.7 at endpoint ($F = 7.17, p < 0.001$), and improvement was significant in each of the three PTSD subscales (reexperiencing, avoidance/numbing, and hyperarousal). Depression and anxiety ratings showed similar improvements, and suicidality ratings did not increase. Global improvement scores decreased from 4.0 at baseline to 2.67 at endpoint ($F = 12.08, p < 0.001$); however, improvement in social and occupational functioning was minimal. Appreciable improvement tended to occur after 6 weeks, suggesting that higher fluoxetine doses and/or duration than that used for depression may be indicated in this population. Panic attack frequency decreased by at least 50% in six of eight patients who kept panic diaries. The high dropout rate reflects problems with side effects, anxiety symptoms, external events, and substance abuse. Our data suggest that fluoxetine is effective in reducing reexperiencing, avoidance, and hyperarousal symptoms of PTSD, and this improvement is independent of comorbid panic disorder. In addition, fluoxetine appears to be effective in reducing panic attacks in PTSD patients. The efficacy of fluoxetine for some PTSD patients is interesting in light of emerging neuropharmacologic data suggesting serotonergic dysregulation in some PTSD patients. Noradrenergic hypotheses are also discussed. The findings should be confirmed by double-blind, placebo-controlled studies.
(J Clin Psychopharmacol 1993;13:107–113)

POSTTRAUMATIC STRESS DISORDER (PTSD) is often a chronic, disabling condition that responds poorly to known treatments. Pharmacologic treatment trials for PTSD have reported some symptom reduction with tricyclic antidepressant agents and monoamine oxidase inhibitors (reviewed in reference 1). Four placebo-controlled studies have been conducted; three studied tricyclic antidepressant drugs (imipramine, desipramine, and amitriptyline), and two studied a monoamine oxidase inhibitor (phenelzine).[1–4] Intrusive symptoms as measured by the Impact of Event Scale (IES) were significantly improved only in the study by Frank and associates[3] of imipramine and phenelzine; IES avoidance did not improve in any study with the exception of a trend in the analysis of Davidson and associates[1] of 8-week completers. Roughly half of these studies found global improvement, and half found significant reduction of depression. Anxiety symptoms did not improve in most studies. Shestatzky and colleagues[2] found gradual improvement over time in both active and placebo groups, and Reist and associates[4] found improvement in anxiety independent of drug or placebo group. The latter two studies were relatively short in duration (5 and 4 weeks, respectively), which may have resulted in a type 2 error.

The inhibition of serotonin reuptake with fluoxetine results in enhanced serotonin function,[5] which is believed to account for its effectiveness in treating major depression (reviewed in references 6 and 7) and probable efficacy for panic disorder[8] and obsessive compulsive disorder.[9] Recent data suggest possible dysregulation in serotonergic and noradrenergic function in PTSD patients[10, 11]; therefore fluoxetine could be effective for PTSD either through direct action on serotonin or secondary effects on noradrenergic systems.[12, 13]

Two published reports suggest that fluoxetine may

Received May 6, 1992, and accepted September 17, 1992.
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be an effective treatment for PTSD. Davidson and associates[14] reported five nonveteran PTSD patients treated with 20 to 80 mg of fluoxetine per day for 8 to 32 weeks. McDougle and associates[15] reported a case series of Veterans Outreach Center patients, using the same dose range for 4 to 48 weeks. Each study reported improvement in both intrusive and avoidant symptoms, and McDougle and colleagues reported that response was independent of comorbid major depression. The findings in our Vet Center population led us to study fluoxetine more rigorously in VA patients, using standardized ratings of PTSD, panic attacks, anxiety, depression, and functional impairment administered pretreatment and weekly for 10 weeks of active medication.

Methods

Patients were recruited from inpatient and outpatient PTSD treatment programs at the West Haven VAMC between May 1990 and May 1991. All patients met DSM-III-R criteria for a current diagnosis of PTSD as determined by the Structured Clinical Interview for DSM-III-R,[16] Clinician-Administered PTSD Scale—Diagnostic Version (CAPS-1),[17] and consensus of the treatment team. Trauma exposure was assessed by the Keane Combat Exposure Scale.[18] Patients were excluded if they had symptoms of psychoactive substance dependence in the previous month, a psychotic disorder, bipolar disorder, previous fluoxetine treatment, or contraindications to the use of fluoxetine.

Symptoms were assessed at baseline and at weekly intervals during the trial. Symptom assessments included two measures of PTSD symptoms—the Clinician Administered PTSD Scale—Weekly Version (CAPS-2) and the IES (severity of each item was scored 0–1–3–5).[19] Because there was no existing instrument designed to measure the weekly frequency and intensity of DSM-III-R symptoms of PTSD in a clinical trial, we used the CAPS-2, a new rating scale developed by the National Center for PTSD (copy of scale available on request). A description of the development and psychometric properties of this instrument will be provided in a separate report.[20]

Depression was rated by use of the 25-item Hamilton Depression Scale (Ham-D),[21] and anxiety was rated by use of the Hamilton Anxiety Scale (Ham-A).[22,23] Patients with comorbid panic disorder completed a weekly panic attack inventory that documented the number and intensity of panic attacks, including limited symptom attacks, per week. Patients with a questionable history of panic attacks were asked to complete the inventory during the initial 2 weeks to rule out panic disorder.

All patients were treated with fluoxetine (20 mg/day) for 4 weeks; the dose was then increased by 20 mg every 2 weeks to a maximum of 80 mg/day until either the response was felt to be optimal or side effects prohibited dose increase. We designed the trial to be 10 weeks in duration for two reasons: (1) because of previous studies indicating that 8 or more weeks may be necessary for an adequate trial in PTSD; and (2) because of the long half-life of fluoxetine,[24] to allow for response at each dose level up to the maximum recommended dose.

Data analysis

A repeated measures analysis of variance (ANOVA) was used to test the statistical significance of symptom change from baseline over time. For purposes of the ANOVA, missing values midtrial were interpolated and the last value was carried forward for patients completing at least 3 but fewer than 10 weeks. We also performed these analyses on 5- and 10-week completers (N = 16 and 10, respectively), and the results were very similar to those for 3-week completers; therefore, only the 3-week completer data are included in this report (additional data available on request). Change over time was considered significant if p was less than 0.05. Comorbid panic disorder was included in the CAPS-2 analysis to test for association with outcome.

To examine the time course of improvement, changes in the CAPS-2 and global improvement ratings were tested for statistical significance for each week versus baseline by the paired t-test, by a two-tailed test with $\alpha = 0.05$. Mean scores and sample size were calculated for each week. Missing values were not estimated.

Treatment response was also assessed with "responder" defined as a 50% decrease in CAPS-2 or IES scores, at least a two-point decrease on the CAPS-2 global improvement rating, and the clinical consensus of two psychiatrists (L.M.N. and C.A.M.). "Partial responder" was defined as meeting some but not all response criteria. Patients who did not meet these criteria were considered nonresponders. χ^2 was used to examine the association of response (including partial) with other variables.

Results

Description of sample

Twenty-seven patients entered the trial; eight dropped out before week 3 and were excluded from the data analysis (two for relapse of psychoactive substance abuse, two for side effects, two for noncompliance with ratings, one for exacerbation of panic attacks, and one for family crisis). The remaining 19 patients completed a mean of 8 weeks (range, 3 to

10). Ten patients completed all 10 weeks. Reasons for failure to complete the full 10 weeks included: two for side effects, two for increased anxiety requiring a second medication, one for side effects and nervousness, two were doing well clinically but were noncompliant with continued weekly visits, one for relapse of psychoactive substance abuse, and one for family problems.

All patients were male combat veterans; 17 served in Vietnam, one in Korea, and 1 in World War II. The average age was 45.1 ± 8.2 years, and the average Combat Exposure Scale score was 30.0 ± 5.5 (level 4, moderately heavy). Eleven patients (58%) had comorbid panic disorder, and 16 (84%) had a current major depressive episode. Fourteen (74%) were outpatients, and 5 (26%) were inpatients. Because this was an open trial, other treatments were not discontinued in five patients (26%; two alprazolam; one imipramine, lorazepam, and trilafon; one methadone; one diphenhydramine), and nine (five inpatients and four outpatients; 47%) were in some form of psychotherapy.

Effects on core PTSD symptoms

Reexperiencing. The results of the ANOVA analysis for the individual, subscale, and total CAPS-2 data are shown in Table 1. The reexperiencing subscale of the CAPS-2 decreased significantly from a mean of 13.4 at baseline to 8.8 at endpoint. All individual symptom scores were lower at endpoint than at baseline, but this change was statistically significant only for distressing memories of the traumatic event(s); improvement did not reach statistical significance for psychologic distress with symbolic reminders, flashbacks, and nightmares. However, improvements in individual CAPS-2 items were usually nonsignificant when the mean baseline score was less than 4, suggesting greater severity may be necessary for adequate power.

The IES-intrusion subscale contains four items related to distressing memories, one for nightmares, and two for psychologic distress with reminders. Consistent with the CAPS-2 reexperiencing ratings, mean IES-intrusion scores decreased significantly from 20.4 at baseline to 11.6 at endpoint (see Table 3).

Avoidance/Numbing. As shown in Table 1, improvement in the avoidance/numbing subscale of the CAPS-2 was statistically significant, dropping from a mean of 26.6 at baseline to 16.3 at endpoint. Five of the seven individual symptoms within this cluster, including avoiding thoughts or feelings associated with the trauma, loss of interest, detachment, restricted affect, and sense of foreshortened future, improved significantly with fluoxetine treatment. The symptoms of avoiding activities that serve as reminders of the trauma and psychogenic amnesia were mild at baseline and did not improve significantly.

The IES-avoidance subscale contains five items related to avoidance of thoughts or feelings, one for avoiding activities that are reminders, one for restricted affect, and one for a sense of unreality about the event. Again, consistent with CAPS-2 findings, the IES-avoidance scores decreased from a mean of 17.7 at baseline to 11.5 at endpoint (see Table 3).

Hyperarousal. Improvement in the hyperarousal subscale of the CAPS-2 was also statistically significant, decreasing from a mean of 24.5 at baseline to 17.7 at endpoint. Reductions were significant for four of the six individual symptoms, including insomnia, anger/irritability, difficulty concentrating, and hypervigilance. The insomnia endpoint scores were not much lower than baseline scores because of an increase in scores during the final weeks of the trial. However, this trend was not observed in the Ham-D sleep ratings (see below). The startle scores and physiologic reactivity in response to trauma reminders did not change significantly.

Effects on associated symptoms

Total Ham-D mean scores decreased from 26.7 ± 8.2 at baseline to 14.1 ± 10.0 at endpoint ($F = 7.65$, $p < 0.001$). Total sleep measures decreased from a mean of 5.3 ± 1.3 at baseline to 3.6 ± 2.2 at endpoint ($F = 3.09$, $p = 0.001$). The greatest improvement appeared to be in difficulty falling asleep (data available on request). Because of recent concern regarding suicidality and fluoxetine, we analyzed the suicide item of the Ham-D and found no increase (baseline mean, 0.11 ± 0.32; endpoint, = 0.06 ± 0.24; $F = 0.81$; p = not significant).

As a measure of general symptoms of anxiety, the Ham-A mean scores decreased from 22.0 ± 8.3 to 12.9 ± 6.8 ($F = 8.31$, $p < 0.001$). Panic attack frequency decreased at least 50% in six of eight patients who kept panic diaries (three patients were noncompliant with this rating).

The CAPS-2 includes eight experimental items, including guilt over acts of commission or omission during the event(s), survivor guilt, homicidality, disillusionment with authority, hopelessness, memory impairment/forgetfulness, sadness/depression, and feeling overwhelmed. Four of these symptoms—guilt over acts, hopelessness, sadness, and feeling overwhelmed—improved during the course of fluoxetine treatment (Table 2). Similar to the core PTSD symptoms, the baseline mean score was less than 3.0 for each rating that did not improve significantly.

Global improvement

PTSD. Total CAPS-2 scores decreased from a mean of

TABLE 1. CAPS-2: individual items, subscales, and total scores

Symptom	Mean Scores (SD)		ANOVA (time)	
	Baseline	Endpoint	*F* value	*p* value
1. Distressing Memories	5.3 (1.2)	3.1 (2.3)	2.38	0.01
2. Distress w/Reminders	3.6 (2.7)	3.2 (2.1)	0.72	0.71
3. Flashbacks	1.5 (2.0)	0.4 (1.1)	0.89	0.54
4. Distressing Dreams	3.1 (2.8)	2.1 (2.3)	1.18	0.31
Reexperiencing Subscale	**13.4 (4.7)**	**8.8 (6.0)**	**2.11**	**<0.05**
5. Avoid Thought/Feel	4.7 (2.1)	2.8 (2.1)	3.47	<0.001
6. Avoid Activities	2.6 (2.5)	1.9 (2.5)	1.05	0.40
7. Psychogenic Amnesia	1.5 (2.0)	1.3 (1.7)	0.73	0.69
8. Loss of Interest	5.2 (1.7)	3.8 (2.3)	2.58	<0.01
9. Detachment	4.4 (2.3)	2.3 (2.4)	2.91	<0.005
10. Restricted Affect	5.2 (1.6)	2.7 (2.8)	5.97	<0.001
11. Foreshortened Future	3.0 (2.9)	1.4 (1.8)	2.51	<0.01
Avoidance/Numbing Subscale	**26.6 (8.7)**	**16.3 (10.7)**	**7.31**	**<0.001**
12. Insomnia	6.5 (1.3)	5.6 (1.7)	3.33	<0.001
13. Anger/Irritability	4.2 (2.1)	2.2 (2.5)	2.20	<0.05
14. Concentration	4.7 (2.0)	3.0 (2.0)	3.08	<0.005
15. Hypervigilance	4.2 (2.0)	2.6 (2.3)	3.60	<0.001
16. Startle	3.1 (2.6)	2.7 (2.2)	1.04	0.41
17. Physio React/Remind	1.8 (2.3)	1.6 (1.9)	1.79	0.07
Hyperarousal Subscale	**24.5 (7.3)**	**17.7 (8.3)**	**4.44**	**<0.001**
Total	**64.5 (14.5)**	**42.7 (20.9)**	**7.17**	**<0.001**

TABLE 2. CAPS-2: experimental item scores

Symptom	Mean Scores (SD)		ANOVA (time)	
	Baseline	Endpoint	*F* value	*p* value
Guilt over acts	4.1 (1.4)	2.1 (1.9)	4.08	<0.001
Survivor guilt	2.7 (2.4)	1.9 (1.8)	0.56	0.84
Homicidality	2.4 (2.6)	1.1 (1.7)	1.49	0.15
Disillusion with authority	2.9 (2.9)	2.2 (2.6)	1.06	0.39
Hopelessness	3.8 (2.7)	1.6 (2.3)	2.73	<0.01
Memory impairment	2.3 (2.4)	1.7 (1.8)	1.55	0.13
Sadness/depression	5.1 (1.2)	2.8 (2.0)	3.61	<0.001
Overwhelmed	3.5 (2.1)	1.9 (1.8)	2.13	<0.05

64.5 at baseline to 42.7 at endpoint, which was statistically significant (Table 1). The effect of comorbid panic disorder was not significant. Analysis of time course showed sustained improvement after week 6. Consistent with the CAPS-2, mean IES total scores decreased from 38.1 at baseline to 23.2 at endpoint (see Table 3).

Overall, the effect of fluoxetine on PTSD was statistically significant. CAPS-2 global improvement ratings dropped from a mean of 4.00 ± 0 to 2.67 ± 0.84 ($F = 12.08$, $p < 0.001$). Improvement from baseline was statistically significant at week 3, but clinically meaningful improvement probably began at week 6.

Functioning. Despite highly statistically significant improvements in many symptom measures, the CAPS-2 rating of the effect of PTSD symptoms on social functioning showed only a modest yet statistically significant decrease from 2.67 ± 0.78 to 2.44 ± 0.86 ($F = 2.42$, $p < 0.05$) and the effect of PTSD symptoms on occupational functioning did not change (2.22 ± 1.06 at baseline, 2.17 ± 1.10 at endpoint; $F = 0.39$, p = not significant).

Response Rate. Seven patients (37%) had a good response, five (26%) had a partial response, and seven (37%) did not benefit at all from fluoxetine. Inpatient status and concurrent medications were not associated with response.

Discussion

Our data show that fluoxetine treatment is effective in reducing many key symptoms of PTSD, and its efficacy was not limited to depression and panic. Reexperiencing and avoidant/numbing symptoms improved on both the CAPS-2 and IES subscales, and CAPS-2-hyperarousal improved. In particular, symptoms specific to PTSD improved, such as intrusive memories and hyper-

Table 3. IES Ratings

Subscale	Mean Scores (SD)		ANOVA (time)	
	Baseline	Endpoint	*F* value	*p* value
Intrusion	20.4 (5.9)	11.6 (8.7)	5.24	<0.001
Avoidance	17.7 (5.7)	11.5 (7.2)	5.72	<0.001
Total	38.1 (9.6)	23.2 (14.9)	7.51	<0.001

vigilance; therefore, efficacy was not limited to PTSD symptoms that overlap with symptoms of major depression.

The amount of reduction in IES scores in this study (40%) is similar to that reported for phenelzine (51%) by Frank and associates,[3] which is the most robust PTSD response cited in the placebo-controlled trials. Improvements in IES scores ranged from 3 to 25% for the other antidepressant agents[1-4] and from slight worsening to 17% in the four placebo-treated groups. If this degree of efficacy is confirmed in placebo-controlled studies of fluoxetine, it would represent an important alternative to current pharmacotherapies for PTSD, particularly for patients who cannot tolerate monoamine oxidase inhibitor side effects or comply with a low-tyramine diet. In addition, fluoxetine may reduce symptoms in the avoidant/numbing cluster, which did not improve significantly with other antidepressant agents. Therefore, fluoxetine may be the drug of choice in PTSD patients with prominent symptoms of numbing, detachment, and avoidance. If a superior efficacy of serotonin-reuptake inhibitors for the avoidant/numbing symptom cluster is confirmed in future studies (as compared with reexperiencing symptoms, which may respond to several classes of antidepressant drugs), it would suggest that there are different neurobiologic mechanisms mediating the expression of these two symptom groups. Because this is the first clinical trial using the CAPS-2, it is not possible to compare degree of efficacy for symptoms of hyperarousal.

Shay[25] observed decreased rage in veterans with PTSD treated with fluoxetine, consistent with our data showing a significant reduction of the anger/irritability rating in the CAPS-2 hyperarousal cluster. In an amitriptyline trial for PTSD, Davidson and associates[1] suggested that frequent panic attacks may be associated with poor treatment response, and conversely, in an open trial of phenelzine, two patients with comorbid panic disorder were among the most improved.[26] However, we found no effect of comorbid panic on improvement in PTSD symptoms.

Several patients did not improve until late in the trial, at doses of 60 or 80 mg/day, but it is unclear whether higher dose or longer duration accounts for efficacy. Our clinical impression is that many PTSD patients treated with lower doses for longer periods of time have required fluoxetine doses of 60 or 80 mg for a robust response. However, this hypothesis needs to be tested in a double-blind dose comparison study.

It should be noted that even the "responders" did not achieve a full remission with absence of PTSD symptoms, as might be seen in the treatment of major depression, but instead had a gradual and incomplete improvement, similar to that seen in obsessive-compulsive disorder.[27]

Despite symptom improvement, considerable functional impairment persisted. It may be that 10 weeks is too short for symptom reduction to be translated into functional improvement. For many patients, disabling symptoms have persisted for 20 years, profoundly affecting relationships with family, friends, and coworkers, as well as functional capability. These long-standing patterns may be slow to reverse or may require specific rehabilitative efforts in addition to pharmacotherapy. Several patients were receiving or applying for service-connected disability. Although there is no evidence that patients would be capable of higher occupational functioning if disability income was not available, this issue is often felt to confound rehabilitation efforts for both financial and psychologic reasons. Because no data on functional impairment are available from previous reports, we are unable to compare our results with those of other trials. It is important to confirm these findings in nonveteran populations encompassing a range of trauma severity and chronicity.

Preclinical studies suggest a role for serotonin (5-hydroxytryptamine; 5-HT) in animal models of mood and anxiety states. In humans, the integrity of 5-HT function has been shown to be necessary for sustained remission of major depression[28,29] and abnormal 5-HT neurotransmission has been hypothesized in the pathophysiology of some anxiety disorders.[30] In an initial study of 5-HT function, some PTSD patients experienced panic attacks and flashbacks when administered a 5-HT agonist, *M*-chlorophenylpiperazine.[11] Some PTSD patients exhibited this response to the α-2-adrenergic antagonist yohimbine[10]; however, preliminary results suggest that there is little overlap between patients who hyperrespond to a noradrenergic antagonist versus a 5-HT agonist. If there are subtypes of PTSD with dysregulation of different neurotransmitter systems, it would be important to identify whether responses to neuropharmacologic challenge tests predict response to different classes of medications.

In addition to the primary action of fluoxetine on 5-HT function, secondary effects on noradrenergic function may account for clinical improvement in these patients. Several lines of research suggest dysregulation of noradrenergic systems in PTSD patients.[10,32] Preclinical studies indicate that increases in 5-HT neuro-

transmission may reduce noradrenergic neuronal activity, e.g., electrical stimulation of the dorsal raphe and iontophoretic application of 5-HT inhibits locus coeruleus firing.[12] A recent clinical study found that the investigational 5-HT reuptake inhibitor fluvoxamine blocks the anxiogenic effect of yohimbine.[13]

Our data suggest notable efficacy when patients receive an adequate trial of fluoxetine for PTSD, given the poor response to treatments studied. However, many patients did not receive an adequate pharmacologic trial because of the side effects, anxiety symptoms, external events, and substance abuse. Our 3-week completer rate (70%) is comparable to the 67 to 87% 4-week completer rate in placebo-controlled studies[1, 2, 4] and much higher than that of a recent open fluvoxamine trial (46%).[32] Our 10-week completer rate was 37% (52% continued medication, but four patients discontinued research ratings). This rate is lower than the 72% who completed 8 weeks in the study of Davidson and associates[1] but is higher than the 21% who completed 9 weeks of open fluvoxamine.[32] Future studies of PTSD should address the ability to tolerate serotonin reuptake inhibitors as compared with other treatments.

The findings of this open fluoxetine trial should be confirmed in a double-blind, placebo-controlled trial. As mentioned above, assessment of the efficacy of fluoxetine for individual symptoms may require a larger sample or greater severity of specific PTSD symptoms. Additional clinical characteristics should be explored for differential treatment response to facilitate treatment selection for a given patient.

Acknowledgment

Presented in part at the 7th Annual Meeting of the International Society for Traumatic Stress Studies, Washington, D.C., October 27, 1991. This study was supported by the National Center for PTSD funded by the Department of Veterans Affairs. The authors thank Elisheva Dan, PA-C, for assistance with data collection and Andreas Nicholau, PhD, for assistance with data analysis.

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Question: What is RPTSD?
Incorrect answer: Recurrent posttraumatic stress disorder.
Correct answer: Robert Post traumatic stress disorder—the condition that ensues when one is asked to explain in detail and critique Post's theories and models of kindling and psychiatric disorders.

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