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FLUVOXAMINE TREATMENT IN VETERANS WITH COMBAT-RELATED POST-TRAUMATIC STRESS DISORDER

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This study was designed to investigate the efficacy of the antidepressant fluvoxamine in the treatment of combat-related post-traumatic stress disorder (PTSD). Fifteen veterans with combat-related PTSD and no other psychiatric diagnosis except depression were recruited to participate in a 14-week open-label study of fluvoxamine. Patients underwent a 30-day washout period and were rated with the Clinician Administered PTSD Scale (CAPS), Mississippi Scale, Beck Depression Inventory (BDI), Hamilton Rating Scale for Depression (HAM-D) and Hamilton Rating Scale for Anxiety (HAM-A) at baseline, and every 2 weeks until week 14. Three patients stopped fluvoxamine prematurely due to side effects and 7 withdrew consent before completing the 14-week trial. Eight patients completed at least 8 weeks of treatment. The total daily dose of fluvoxamine ranged from 100 to 300 mg with a mean daily dose of 150 mg at week 14. Intent-to-treat analysis revealed a significant improvement in total CAPS scores, and in the intrusion and the avoidance/numbing subscales. The CAPS hyperarousal scores did not change significantly. HAM-A score also improved significantly. No significant changes were seen on the Mississippi scale, HAM-D, or Beck Depression Inventory in the intent-to-treat analysis. In summary, our study shows that fluvoxamine appears to improve combat-related PTSD symptoms but not depressive symptoms. The high attrition rate and lack of a placebo group limits the conclusions of our study. Controlled studies of fluvoxamine in the treatment of PTSD are warranted. Depression and Anxiety 15:29–33, 2002.

Key words: ***fluvoxamine; post-traumatic stress disorder; pharmacotherapy; open label; major depression***

INTRODUCTION

The search for effective pharmacological treatments for post-traumatic stress disorder (PTSD) has intensified recently with the advent of new pharmacological agents. In a recent review for the formulation of treatment guidelines for PTSD [Foa et al., 2000], antidepressants remain the best studied and most efficacious agents, with the group of selective serotonin reuptake inhibitors (SSRI) emerging as the first line pharmacological intervention [Foa et al., 2000]. Four randomized controlled trials of SSRI have supported this recommendation. Most Recently, Brady et al. [2000] reported a 12-week double-blind, placebo-controlled trial of sertraline in 187 subjects, mostly with civilian-type trauma, and found that sertraline was safe and effective in the treatment of PTSD. Connor et al., [1999] reported a 12-week controlled trial of fluoxetine in 53 subjects with civilian-type trauma, and found fluoxetine superior than placebo. Previously, van der Kolk et al. [1994] reported a 5-week randomized, double-blind trial of fluoxetine in 64 subjects, and found fluoxetine to be effective, particularly in the noncombat-related PTSD subjects. More recently, Hertzberg et al. [2000] reported a 12-week placebo-

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controlled study of fluoxetine in combat-related PTSD and found no significant improvement. Fluvoxamine, another SSRI, has shown promising results in 4 uncontrolled studies of PTSD. Two of these trials have been conducted in combat-related PTSD, and the results have been encouraging. Marmar et al. [1996] reported excellent response and good tolerance in a 10-week open-label trial of fluvoxamine in 10 subjects with combat related PTSD. De Boer et al. [1992] reported a 12-week open-label trial of fluvoxamine in 24 subjects with chronic combat-related PTSD and found modest improvement. In an 8-week open-label trial of 15 subjects with noncombat PTSD, Davidson et al. [1998] reported significant changes across time in 6 efficacy scales, which included a 64.2% overall response in the Duke Global Rating Scale for PTSD (DGRP). In a more recent 10-week open-label trial of fluvoxamine in 16 subjects with noncombat PTSD, Tucker et al. [2000] found fluvoxamine to be effective in both self-reported symptoms scales as well as physiological measures of autonomic reactivity. Encouraged by this promising preliminary data, especially in the more treatment-resistant combat-related PTSD, we decided to investigate the effect of fluvoxamine in a group of subjects with chronic combat-related PTSD and no psychiatric comorbidity except depression.

TABLE 1. Demographic information

Demographic variable	Total n = 15	Non-completers n = 10	Completers n = 5	*P**
Age average (SD)	47 ± 3	48 ± 4	46 ± 1	0.13
Race				0.51
Caucasian	60%	60%	60%	
Hispanic	33%	40%	20%	
Native American	7%	0%	20%	
Marital status				0.48
Married	40%	50%	20%	
Single	7%	0%	20%	
Divorced	47%	40%	60%	
Widowed	7%	10%	0%	
Employment				1.0
Employed	27%	30%	20%	
Unemployed	73%	70%	80%	
Education				0.28
High School or GED	33%	40%	20%	
Some college	47%	50%	40%	
College graduate	20%	10%	40%	

**Fisher's exact test performed on all data except* t*-test with Satterthwaite's correction for age and Jonckheere-Terpstra test of trend for education.*

METHODS

PARTICIPANTS

Fifteen subjects were recruited from the Albuquerque VAMC. All subjects were male Vietnam combat veterans and met the Diagnostic and Statistical Manual-Third Edition-Revised (DSM-III-R) [APA, 1987] criteria for PTSD as determined by the Structured Clinical Interview for DSM-III-R (SCID module for PTSD) [Spitzer and Williams, 1985]. Subjects with active serious medical disorders were excluded from the investigation. Subjects were also excluded if they met diagnostic criteria for antisocial, borderline personality disorders, obsessive compulsive disorder, panic disorder, bipolar disorder, social phobia, and any history of current psychotic features as determined by the SCID-II [Spitzer et al., 1990b] for personality disorders and the Structured Clinical Interview for DSM-III-R, Patient Version (SCID-P) [Spitzer et. al, 1990a]. Subjects who met diagnostic criteria for major depression or dysthymia were allowed into the study. Subjects were required to have a 6-month abstinence period if they had past diagnosis of alcohol or substance abuse or dependence disorder. Subjects meeting inclusion criteria were asked to participate and signed Institutional Review Board-approved informed consent. At the time of the study, no subjects were undergoing adjunctive individual or group psychotherapy. Demographic information is presented in Table 1.

MEASURES AND PROCEDURES

Subjects went through a 30-day washout period prior to entering the study and were allowed to take only chloral hydrate for nighttime sedation during this period. The extended washout period and many of the axis I and II disorders were exclusionary for this trial due to the fact that this study was part of a larger research project aimed at relating platelet serotonin activity to treatment response. At initial screening, subjects signed the consent form and were evaluated by a research team psychiatrist, to ascertain study eligibility. On the next screening visit, subjects were administered the SCID-P [Spitzer et al., 1990a] and SCID-II [Spitzer et al., 1990b]. Subjects completing the washout period were started on fluvoxamine 50 mg BID. Dosage was titrated by the investigator at a rate of 50 mg every seventh day until a therapeutic dose was established within a daily range of 100–300 mg. Compliance was determined by patient interview and pill count of medication returned at each visit. Concomitant medications were kept at a minimum. Chloral hydrate or temazepam were used for nighttime sedation and low-dose lorazepam (1 to 3 mg daily) was used for anxiety during active treatment. Subjects were administered the Clinician Administered PTSD Scale (CAPS) [Blake et al., 1990], the 17-item Hamilton Rating Scale for Depression (HAM-D) [Hamilton, 1960], 14-item Hamilton Rating Scale for Anxiety (HAM-A) [Hamilton, 1959], 21-item Beck Depression Inventory (BDI) [Beck, 1978], 35-item Mississippi Scale for Combat-Related PTSD [Keane et al., 1988], on the first day of treatment (day 1), weeks 2, 4, 6, 8, 10, 12, and 14. All assessments were performed by an experienced rater, trained in the administration of all the instruments used in the study (L.A.C). The rater was not blind to the medications that the subjects were receiving. Symptom change was determined by comparing baseline scores with scores

at post-treatment using a two-tailed paired *t*-test. An intent-to-treat analysis was performed.

RESULTS

Additional diagnosis in the sample included major depression (80%) and dysthymia (7%). Two subjects (13%) had no other diagnosis. Of the 15 subjects entering the study, eight subjects completed at least 8 weeks of treatment with five of those completing the study. Three subjects stopped taking fluvoxamine due to adverse experiences prior to week 14. One subject discontinued due to increased anxiety, nausea, increased perspiration, and dizziness, another because of nausea and dizziness, and the third stopped due to nausea and constipation. One subject was lost to follow-up after 1 week of treatment. One subject was discontinued due to a drug overdose with chloral hydrate, which was deemed by the investigator as a suicidal gesture. The subject was hospitalized and recovered without sequelae. Four subjects withdrew consent because of lack of perceived therapeutic benefit and one because of unwillingness to follow protocol guidelines. The total daily dose of fluvoxamine ranged from 100 mg to 300 mg with a mean daily dose of 150 mg at week 14. Of the 15 subjects entering the study, four subjects were on no psychotropic medications during open-label treatment, six took chloral hydrate, two took chloral hydrate and lorazepam, one took chloral hydrate initially but switched to temazepam during the last 4 weeks of open-label treatment, one took chloral hydrate, but also took temazepam for 4 days during the trial, and one took chloral hydrate and lorazepam with the chloral hydrate later switched to temazepam.

Intent to treat analysis revealed a significant improvement in CAPS total score and all its subscales, except for the hyperarousal (see Table 2). HAM-A score was also reduced significantly in the intent-to-treat analysis. No significant differences were seen in the Mississippi Scale scores or in the depression measures (HAM-D and Beck) in the intent-to-treat analysis. A graph showing the total CAPS scores for each subject across visits is included (Fig 1). There were no statistically significant differences in baseline scores between completers and noncompleters across all rating scales (*t*-test, all *P*-values are greater than 0.22). Similarly, no statistical differences in demographic variables between completers and noncompleters were noted (see demographic variable, Table 1).

TABLE 2. Psychiatric rating scale scores: means, standard deviations, paired *t*-test values

Scales	Day 1 (n = 14)	Final (n = 14)	Difference at final (n = 14)[b]
HAM-D[a]	19.4 ± 1.2	16.2 ± 1.8	–3.1 ± 1.8
HAM-A	20.4 ± 5.8	16.5 ± 9.2	–3.1 ± 2.5**
CAPS (total)	87.6 ± 5.5	55.9 ± 7.7	–30.7 ± 4.7**
CAPS-Intrusion	18.3 ± 2.0	10.2 ± 2.5	–7.5 ± 1.6**
CAPS-Avoidance	38.4 ± 2.3	25.5 ± 3.4	–12.5 ± 2.5**
CAPS-Hyperarousal	31.0 ± 2.0	20.6 ± 2.3	–10.6 ± 2.0
Mississippi	137.6 ± 4.1	133.0 ± 5.5	–3.5 ± 2.7
Beck	33.8 ± 3.1	29.5 ± 4.3	–4.1 ± 2.1

[a]HAM-D, Hamilton Depression Scale; HAM-A, Hamilton Anxiety Scale; CAPS, Clinician Administered PTSD Scale; Mississippi, Mississippi Scale for Combat-Related PTSD; Beck, Beck Depression Inventory.

[b]The mean number of weeks completed that constitute "Final" is 8.4 with a standard deviation of ± 5.35.

*P < .05.

**P < .001.

DISCUSSION

Despite a high attrition rate, our study showed significant improvement in PTSD symptoms with fluvoxamine. Total CAPS scores, intrusion and avoidance/numbing scores improved significantly in the intent-to-treat analysis. The CAPS hyperarousal scores did not change significantly. The HAM-A score showed significant improvement. No significant changes were seen in the Mississippi scores or in the measures for depression (Beck and HAM-D). The discrepancy in treatment response between PTSD and depression has been reported before in controlled studies conducted with phenelzine, imipramine, and placebo [Frank et al., 1988] and Southwick et al.'s [1994] quantitative analysis of 15 clinical trials with tricyclic anti-depressant (TCA) and Monoamine Oxidase Inhhibitors (MAOIs), reporting a greater effect on PTSD symptoms than on depression. However, controlled studies with desipramine and amitryptyline showed a significant antidepressant effect with minimal effects on PTSD symptoms [Davidson et al., 1990,1993; Reist et al., 1989]. Recent SSRI trials have shown an effect in depression as well as PTSD symptoms [van der Kolk et al., 1994; Brady et al., 2000]. These contradictory findings suggest that depression in PTSD might differ from primary depression in its treatment response.

The positive response to fluvoxamine in this study is especially encouraging given the chronicity and treatment resistance of subjects with combat-related PTSD as shown in several studies. Our results are less dramatic than the ones reported by Marmar et al. [1996]; however, in that study 90% of the subjects were employed, in contrast with 27% of our subjects. Presumably Marmar's subjects had higher baseline global functioning, which could account for the better response. Our results were closer to the ones obtained by De Boer et al. [1992], showing modest improvement. The study by Davidson et al. [1998] showed the best response to fluvoxamine in several measures of PTSD, which is consistent with the better outcomes reported in civilian versus combat-related PTSD.

The most important limitation of our study is the lack of a placebo control group. Another limitation is the very high dropout rate. Some possible explanations for this problem include subject's perceived lack of efficacy and side effects (mostly gastrointestinal and dizziness). Concurrent medications were only chloral

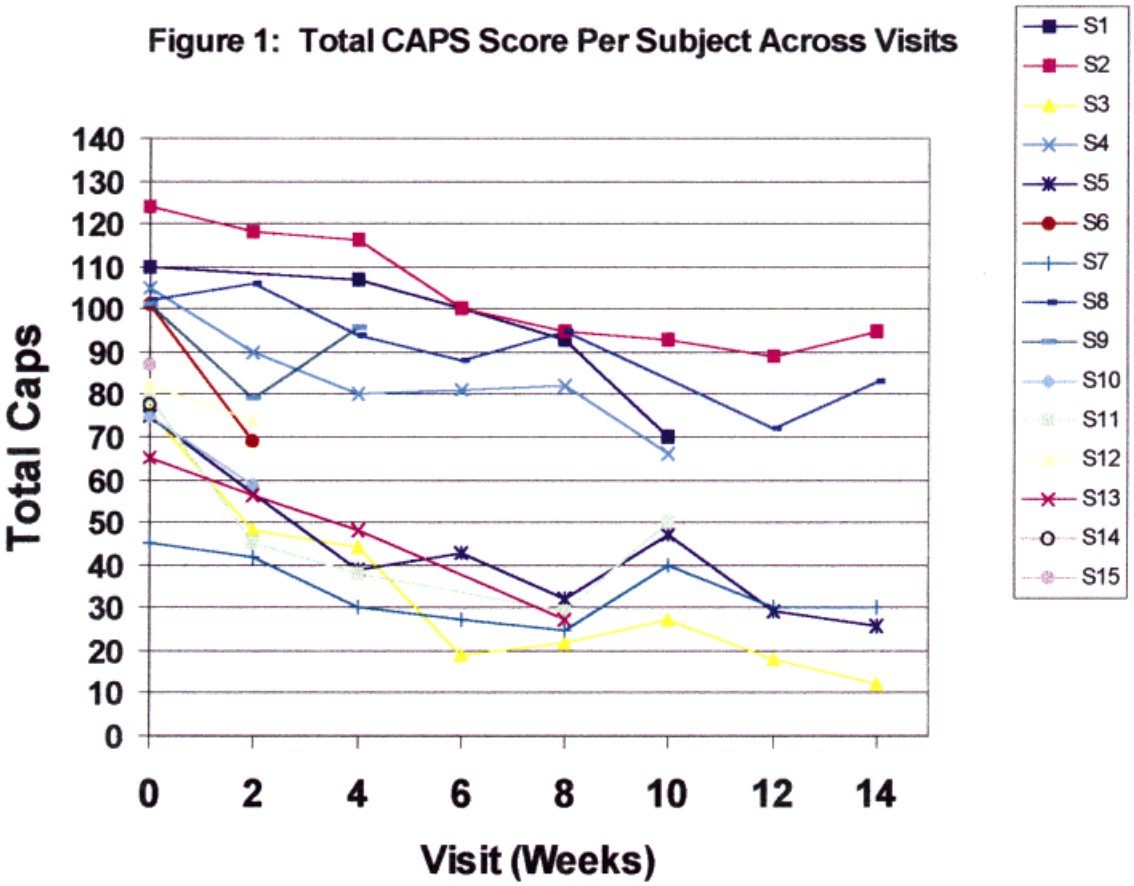

Figure 1. Total Clinician Administered PTSD Scale (CAPS) score per subject across visits. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

hydrate and benzodiazepines for some of the subjects. This could have affected the PTSD and the depressive symptom ratings. However, based on the limited available data on benzodiazepines in PTSD, only sleep seems to improve and not the core PTSD symptoms. In addition, the cohort of patients selected for this trial may be somewhat unique in that they were abstinent of alcohol and drugs for 6 months and did not have other psychiatric diagnosis except for depression. Controlled studies of fluvoxamine in the treatment of PTSD are warranted.

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