

Tolerability of fluoxetine in posttraumatic stress disorder

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Abstract

Purpose: In response to earlier reports that raised concerns about the tolerability of fluoxetine in the treatment of posttraumatic stress disorder (PTSD), this study was conducted to systematically delineate treatment-emergent symptoms (TES) associated with fluoxetine treatment of PTSD. **Methods:** Sixty-five patients with PTSD enrolled in one of two identical-protocol, 12-week studies and received double-blind fluoxetine or placebo. TES data were obtained using a patient-rated checklist, Severity of Symptoms Scale (SOSS). **Results:** Only a single patient discontinued treatment due to medication side effects. Compared to placebo, only three statistically significant TES (nausea, diarrhea, and thirst) occurred more frequently in fluoxetine subjects. Fluoxetine was not associated with any statistically significant activating effects. There were no statistically significant associations between the total number of TES experienced and treatment, gender, or comorbid depressive or panic disorders. **Conclusions:** This systematic assessment of TES indicated that PTSD patients tolerated fluoxetine well without pronounced activating side effects. © 2001 Elsevier Science Inc. All rights reserved.

Keywords: Adverse events; Fluoxetine; Posttraumatic stress disorder; Selective serotonin reuptake inhibitor; Side effects

1. Introduction

Early placebo-controlled pharmacologic trials in posttraumatic stress disorder (PTSD) revealed that amitriptyline (Davidson et al., 1990), imipramine, and phenelzine (Kosten et al., 1991) could each produce some significant beneficial effects in certain PTSD populations. However, each of these agents has shown problems with either incomplete efficacy in PTSD or side effect and safety concerns limiting clinical utility. Other investigations have examined selective serotonin reuptake inhibitors (SSRIs) (Brady et al., 2000; Hidalgo and Davidson, 2000) as well as other recently available antidepressants including nefazadone (Hidalgo et al., 1999), mirtazapine (Connor et al., 1999a), and bupropion (Canive et al., 1998) in the treatment of PTSD. However, the majority of these studies have been uncontrolled, and systematic investigation to discern how well

each of these medications is tolerated by PTSD patients has been largely unexplored.

The side effect profile of fluoxetine is well known generally, but most available adverse event data are derived from studies in depression, obsessive-compulsive disorder, and bulimia nervosa, and little is known about tolerability of this drug specifically in PTSD. However, agitation, anxiety, and other activating effects have been reported in uncontrolled trials of fluoxetine in PTSD. In one open prospective fluoxetine trial with 27 combat veteran subjects with PTSD (Nagy et al., 1993), 30% of subjects reportedly discontinued treatment because of increased anxiety, nervousness, exacerbation of panic attacks, and/or other side effects. Interestingly, 58% of the patients in that study had the comorbid diagnosis of panic disorder and 84% was experiencing a current major depressive episode. Additional open trial results have also suggested that the presence of comorbid panic disorder may predispose PTSD patients to experience activating effects from fluoxetine (Marshall et al., 1995). In contrast, other uncontrolled trials of fluoxetine in PTSD have connoted better tolerability. In one of these studies (McDougle et al., 1991), 87% of 23 male veteran patients with PTSD completed at least a 4-week trial of fluoxetine, and only a single patient dropped out because of side effects

Abbreviations: PTSD; posttraumatic stress disorder; SOSS, Severity of Symptoms Scale; TES, treatment-emergent symptoms

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(dyspepsia); although 70% of the subjects had comorbid depression, no mention of comorbid panic disorder was made. Another investigation, which concluded that fluoxetine reduced explosiveness and elevated mood in 28 combat veterans (Shay 1992), also suggested good overall tolerability, stating that fluoxetine had “fewer and more acceptable side effects [than sedating antidepressants],” and reporting the most frequent side effect (57%) to be increased insomnia. The first published placebo-controlled investigation of fluoxetine in PTSD (van der Kolk et al., 1994) concluded that fluoxetine is an effective pharmacotherapeutic agent for the treatment of PTSD and its associated features, yet the study was criticized (Cohen, 1995) for not fully explaining the high (26.6%) dropout rate. Whether or not the dropouts were due to side effects was not specifically discussed in the published report of the study.

With the above considerations in mind, the goal of this report is to more accurately clarify how well PTSD patients tolerate fluoxetine by examining data derived from two recent studies with identical protocols. In one of these studies, a placebo-controlled investigation of 53 civilian PTSD patients ($n_{\text{fluoxetine}}=27$; $n_{\text{placebo}}=26$), Connor et al. (1999b) demonstrated that fluoxetine produced statistically and clinically significant improvement on all evaluated measures of PTSD severity. In the other study, a concurrent parallel trial of 12 male combat veterans with PTSD ($n_{\text{fluoxetine}}=6$; $n_{\text{placebo}}=6$), subjects did not experience significant benefit from fluoxetine treatment (Hertzberg et al., 2000). In order to assess tolerability, treatment-emergent symptoms (TES) were recorded in both studies using a Severity of Symptoms Scale (SOSS). This scale had the advantage of providing numerical data reflecting TES severity levels that allowed for subsequent systematic statistical analyses. We report here an assessment of the tolerability of fluoxetine in PTSD using these SOSS results.

2. Methods

2.1. Subjects

Both studies were approved by local institutional review boards (IRBs) and all subjects provided written informed consent. Included in the study were those patients who met DSM-III-R (American Psychiatric Association, 1987) criteria for PTSD, according to the Structured Clinical Interview for the DSM-III-R (SCID) (Spitzer et al., 1988) and the revised Structured Interview for PTSD (SIP) (Davidson et al., 1997). Additional information about inclusion and exclusion criteria and the study design is given elsewhere (Connor et al., 1999b).

2.2. Collection of TES data

At baseline and at each subsequent study visit, subjects completed the 32-item self-rated checklist SOSS to measure

and record TES. Subjects rated the severity level for each symptom listed on the form by scoring (checking) either 0 (*none*), 1 (*mild*), 2 (*moderate*), or 3 (*severe*). The SOSS has been used in other studies (Davidson et al., 1993) and appears to have face validity.

2.3. Assessment of activation effects

From the full SOSS, eight items were designated to represent a set of activation symptoms: “trembling,” “heart racing or pounding,” “sweating,” “poor sleep,” “nightmares,” “muscle twitching or clenching,” “spasms or drawing of the muscles,” and “uncomfortable urge to move about.” In order to evaluate whether or not PTSD patients with high pretreatment levels of hyperarousal symptoms were more likely to develop any of these eight activation symptoms from fluoxetine treatment during the study, analyses were performed utilizing baseline data collected from the SIP scale. The interviewer-rated, 17-item SIP scale includes one item (item B5) that requests an answer to the question: “Does exposure to an event that reminds you of, or resembles, the [traumatic] event cause you to have any physical response? (sweating, trembling, heart racing, nausea, hyperventilation, dizziness, etc.)” Responses to item B5 were rated numerically from 0 to 4 based on severity. Subjects with baseline item B5 responses of ≥ 3 were considered to represent a group with high baseline hyperarousal symptoms, while those with responses of ≤ 2 represented a low baseline hyperarousal symptom group. Using these criteria, relationships between high and low baseline hyperarousal symptom levels and the emergence of activation TES during subsequent treatment were explored statistically.

2.4. Drug administration: dosing and standardization of data collection

After subjects were randomized to receive double-blind fluoxetine or matching placebo, the dose was begun with one 10-mg pill (or placebo equivalent) per day, and increased at a rate of 10 mg/week to a maximum of 60 mg/day as clinically indicated and tolerated. Compliance was assessed by pill counts and daily logs were maintained by subjects. Medications were administered in accordance with a manual of standardized directions including specific questions about side effects that were reviewed with subjects at each visit.

2.5. Data analysis

Two different criteria to define what constitutes a TES were developed. The more restrictive criterion defines a TES as any increase in severity value (compared to the baseline value) of a magnitude of two or greater (≥ 2) for a given symptom item on the SOSS at any time during the study. The less restrictive criterion defines a TES as

any increase in value of one or greater (≥ 1) at any time during the study. Results of data analyses using each of these two criteria were compared. TES data were also analyzed to identify how many TES ultimately resolved by study's end. Resolution of a TES was defined as the converse of the original TES definition itself: a subsequent decrease in the severity value recorded for a particular TES of either two or more (≥ 2) points or one or more (≥ 1) points, respective to the TES definition used, constituted resolution.

TES rates, expressed as percentages, for each SOSS item were determined separately for both active medication and placebo subject groups. Results were then subjected to comparative analyses to identify symptoms associated with statistically significant differences between active medication and placebo. The total number of TES (TES Total) experienced, which potentially could range from 0 to 32, was determined for each subject. Several variables within the study sample were identified (e.g., gender, presence or absence of comorbid panic or major depressive disorders, and number of comorbid Axis I or II disorders) and mean TES Total values for groups based on these variables were determined. Statistical analyses were performed to discover if any of these variables was associated with higher or lower mean TES Total values. Sexual side effects were measured according to two items on the SOSS—"difficulty achieving orgasm" and "difficulty having an erection"—though the second was applicable to males only.

Data were analyzed using *t* tests, chi-square (χ^2) tests, and Fisher exact tests as appropriate, as well as Spearman and Pearson coefficients, where indicated. Statistical significance was set at the 5% level ($P \leq .05$).

3. Results

3.1. Discontinuation rates and doses

Of the 65 subjects (33 in the fluoxetine group and 32 in the placebo group), 18 (28%) discontinued treatment before the end of the study: 21% of fluoxetine patients and 34% of placebo patients discontinued early. Only one early dropout (from the veteran sample) was due to medication side effects (activation symptoms) on fluoxetine 10 mg/day. All other patients in the veteran sample ($n=12$; six on fluoxetine and six on placebo) completed the full 12 weeks of the study. Of 17 early dropouts from the civilian sample, 6 (35%) were from the fluoxetine group and 11 (65%) were from the placebo group. Reasons for dropout in the fluoxetine group included lack of efficacy ($n=1$), loss to follow up ($n=3$), relocation ($n=1$), and protocol violation ($n=1$: repeated nonattendance); subjects in the placebo group who dropped out did so due to lack of efficacy ($n=5$), loss to follow up ($n=1$), relocation or job concerns ($n=3$), and protocol violation ($n=2$: noncompliance and initiation of prohibited nonprotocol antidepressant medication).

Daily fluoxetine doses ranged from 10 to 60 mg. In the civilian sample, the median daily dose was 30 mg in the active drug group and "40 mg" in the placebo group. The mean daily fluoxetine dose at endpoint for the combat veteran sample was 48 mg.

3.2. TES results

3.2.1. Statistically significant TES

When a TES was defined as any increase of ≥ 2 points above baseline at any time during the study, only a single SOSS item, "nausea," emerged as a statistically significant fluoxetine-associated TES as compared to placebo ($\chi^2=6.52$, $df=1$, $P=.01$). Using the more permissive ≥ 1 point TES criterion, the "diarrhea" ($\chi^2=5.22$, $df=1$, $P=.02$) and "thirst" ($\chi^2=8.07$, $df=1$, $P=.005$) SOSS items additionally emerged as statistically significant (fluoxetine > placebo), with the "nausea" item maintaining statistical significance ($\chi^2=4.98$, $df=1$, $P=.03$). Interestingly, with the ≥ 1 criterion, the SOSS "rash" item was a statistically more frequent TES in the placebo group than in the fluoxetine group ($\chi^2=4.24$, $df=1$, $P=.04$). Table 1 lists TES incidence values for SOSS items in which statistically significant differences between fluoxetine and placebo were identified.

3.2.2. Resolution of TES

Of the fluoxetine patients who experienced any statistically significant TES, most subsequently exhibited resolution (decrease of severity score back to at least the baseline value) of those TES by the end of the study. Table 2 lists the rate of resolution for each of the statistically significant TES.

3.2.3. Comorbid panic disorder and activating effects

In the fluoxetine group, compared to patients without panic disorder ($n=28$), subjects with comorbid panic dis-

Table 1
Statistically significant TES from the SOSS using two different TES criteria: fluoxetine ($n=33$) versus placebo ($n=32$)

SOSS items ^a	Percent of subjects reporting TES			
	≥ 2 point TES criterion data ^b		≥ 1 point TES criterion data ^c	
	Fluoxetine (%)	Placebo (%)	Fluoxetine (%)	Placebo (%)
Nausea	30	6	57	31
Diarrhea	–	–	51	25
Thirst	–	–	51	19
Rash ^d	–	–	6	25

"–" indicates data not presented because TES fluoxetine/placebo differences were not statistically significant

^a Only those SOSS items that showed statistically significant differences in TES rates between fluoxetine and placebo are listed.

^b TES defined as any increase of ≥ 2 points (as compared to baseline) at any time during the study.

^c TES defined as any increase of ≥ 1 point (as compared to baseline) at any time during the study.

^d Placebo > fluoxetine.

Table 2

Resolution of statistically significant TES from the SOSS using two different TES/resolution criteria: fluoxetine versus placebo

TES ^a	Subjects experiencing resolution of TES							
	≥2 point TES criterion data ^b				≥1 point TES criterion data ^c			
	Fluoxetine		Placebo		Fluoxetine		Placebo	
	Resolved (%)	(<i>n_R</i> / <i>n_{TES}</i>) ^d	Resolved (%)	(<i>n_R</i> / <i>n_{TES}</i>)	Resolved (%)	(<i>n_R</i> / <i>n_{TES}</i>)	Resolved (%)	(<i>n_R</i> / <i>n_{TES}</i>)
Nausea	80	(8/10)	100	(2/2)	68	(13/19)	70	(7/10)
Diarrhea	–	–	–	–	47	(8/17)	50	(4/8)
Thirst	–	–	–	–	59	(10/17)	83	(5/6)
Rash	–	–	–	–	0	(0/2)	75	(6/8)

“–” indicates data not presented because TES fluoxetine/placebo differences were not statistically significant

^a Only those SOSS items that showed statistically significant differences in TES rates between fluoxetine and placebo are listed.

^b TES defined as any increase of ≥2 severity score points (as compared to baseline) at any time during the study; resolution defined as any subsequent decrease of ≥2 severity score points.

^c TES defined as any increase of ≥1 severity score points (as compared to baseline) at any time during the study; resolution defined as any subsequent decrease of ≥1 severity score points.

^d *n_{TES}* indicates number of subjects who experienced SOSS symptom item as a TES; *n_R* indicates number of subjects who subsequently experienced resolution of that TES by the end of the study.

order (*n*=4) appeared somewhat more likely to experience “sweating” as a TES when the ≥2 point criterion was used, but this was not statistically significant and the association was even less evident with the ≥1 criterion data. “Trembling” also occurred more commonly in panic disorder patients (≥1 and ≥2 criteria), but this was not statistically significant. Panic disorder subjects also appeared to exhibit some increased tendency to experience “poor sleep” (≥1 point criterion), but this too was not statistically significant.

3.2.4. Evaluation of activating TES

Of the eight SOSS items identified as activation symptoms (see Methods), several showed somewhat higher TES incidence rates in the fluoxetine group, but for other activation symptoms, incidence rates were higher in the placebo group; furthermore, in some instances, results based on the ≥1 point TES criterion were in apparent conflict with results based on the ≥2 point criterion. However, none of the fluoxetine/placebo differences for these eight activation symptoms was statistically significant. Subjects with high baseline physiological hyperarousal scores (≥3) on the SIP item B5 (see Methods) did not exhibit an increased tendency to experience more activation TES as compared to subjects with low baseline hyperarousal scores. In fact, there was some increased tendency for subjects with low baseline levels of hyperarousal symptoms to develop one activation TES (“muscle twitching”) during the study, although this observation was not significantly significant.

3.2.5. Sexual side effects

The data revealed an 18% (≥2 criterion) to 33% (≥1 criterion) incidence rate for “difficulty achieving orgasm” in fluoxetine subjects, as compared to 12–15% for placebo subjects, respectively. The rate for “difficulty having an erection” was 8% (≥2 criterion) to 25% (≥1 criterion) for male fluoxetine subjects, compared to 0–25% for placebo,

respectively. None of these fluoxetine/placebo differences was found to be statistically significant.

4. Discussion

In contrast to concerns raised in some other studies about a particular tendency for fluoxetine to produce problematic activation effects in PTSD patients, data from this study do not emphasize such a propensity. None of the TES in this study was serious, and overall fluoxetine was safe and well tolerated. The 27% dropout rate observed is not considered unduly high for a 12-week-long study of PTSD, and subjects taking fluoxetine were less likely to dropout than those taking placebo. Only a single patient discontinued because of adverse medication effects (activation), which translates into a relatively low cause-specific discontinuation rate of about 3.3%. Furthermore, subjects with high baseline levels of hyperarousal did not show any increased likelihood of experiencing activation TES. Subjects with panic disorder showed some increased tendency to experience trembling, poor sleep, and sweating as TES, but these observations were not statistically significant; however, since the number of subjects with comorbid panic disorder in our sample was fairly small, it is possible that this subgroup may have exhibited statistically significant activation TES if it had included a larger number of patients with comorbid panic disorder.

It is important to recognize that several DSM-IV terms used to delineate core PTSD symptoms are similar to terms frequently employed to depict potential pharmacological side effects. As a result, confusion could occur about whether symptoms emerging or worsening during the course of treatment are attributable to medication effects or to PTSD itself. Direct comparisons of TES between patients on active medication and those on placebo help to clarify this. Moreover, the process of elucidating side effects

may be enhanced by establishing baseline levels of symptom severity and subsequently assessing TES severity levels throughout the course of treatment using an instrument such as the SOSS.

5. Conclusions

This placebo-controlled investigation of treatment-emergent effects suggests good overall tolerance of fluoxetine in patients with PTSD. While it may be appropriate to exercise increased attentiveness when treating PTSD patients with comorbid panic symptoms, these data provide no compelling reason to avoid using fluoxetine as a first-line treatment for these patients.

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