Brief report

A pilot randomized controlled trial with paroxetine for subthreshold PTSD in Operation Enduring Freedom/Operation Iraqi Freedom era veterans


1. Introduction

The specific constellations of symptoms characterizing subthreshold posttraumatic stress disorder (PTSD) have been variously described (Blanchard et al., 1994; Carlier and Gersons, 1995; Marshall et al., 2001a, 2001b; Stein et al., 1997; Weiss et al., 1992), but individuals with subthreshold PTSD have generally been characterized as having experienced a traumatic event and subsequently reporting some, but not all, symptoms that are consistent with PTSD (i.e. not meeting criteria for “full” PTSD). The prevalence of subthreshold PTSD (sometimes referred to as “partial PTSD”) appears comparable to full PTSD, and converging evidence suggests that subthreshold PTSD conditions are clinically important and associated with social, occupational, and functional impairment (Marshall et al., 2001, 2001b; Stein et al., 1997). Individuals with subthreshold PTSD symptoms also appear to be at increased risk for developing comorbid depressive disorders and suicidal ideation (Marshall et al., 2001). Further, Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) era veterans with subthreshold PTSD were more likely to report suicidal ideation and hopelessness compared to veterans without PTSD, and there were also no differences in these clinical symptoms between veterans with subthreshold PTSD and veterans meeting full criteria for PTSD (Jakupcak et al., 2011). Moreover, OEF/OIF veterans with subthreshold PTSD report similar elevated incidents of aggression compared to OEF/OIF veterans with full PTSD (Jakupcak et al., 2007). Degree of impairment increases as the number of PTSD symptoms increases (Marshall et al., 2001), and subthreshold PTSD symptoms may progress to full PTSD (Carty et al., 2011). However, even if subthreshold symptoms do not progress to full PTSD, the associated impairment of subthreshold PTSD can be substantial, with significant and prolonged effects (Cukor et al., 2010). The treatment of subthreshold PTSD thus merits further investigation.

No reported pharmacological intervention studies have specifically targeted patients with subthreshold PTSD to date. Investigations in subthreshold PTSD might logically consider an agent with known efficacy for full PTSD, such as paroxetine (Marshall et al., 2001a,b; Tucker et al., 2000), which is FDA-approved for PTSD. We thus conducted a pilot randomized controlled trial (RCT) with paroxetine for subthreshold PTSD in Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) era veterans. Hospital Anxiety and Depression Scale (HADS) scores improved by 30.4% in the paroxetine group. Paroxetine may have promise for subthreshold PTSD.

Keywords:
PTSD
Subthreshold
Paroxetine

Abstract

Subthreshold posttraumatic stress disorder (PTSD) is associated with increased risk for suicidality, depression, and functional impairment. We thus conducted a small (N=12) pilot randomized controlled trial (RCT) with paroxetine for subthreshold PTSD in Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) era veterans. Hospital Anxiety and Depression Scale (HADS) scores improved by 30.4% in the paroxetine group. Paroxetine may have promise for subthreshold PTSD.
already developed subthreshold PTSD and who have been symptomatic for several months or longer.

2. Methods

2.1. Study design

This pilot randomized, placebo-controlled, double-blind, 12-week trial of paroxetine was conducted at the Durham Veterans Affairs Medical Center (Durham VAMC) in Durham, NC (ClinicalTrials.Gov number NCT00560937). Patient enrollment occurred from February 2006 through July 2008. This study was approved by the Durham VAMC Institutional Review Board. All patients provided written informed consent.

2.2. Participants

OEF/OIF era veterans, between the ages of 18 and 55, who served in the US military since September 11, 2001, and who met criteria for subthreshold PTSD defined as: meeting Criterion A (exposure to a traumatic event) and demonstrating at least one symptom (frequency ≥ 1, and intensity ≥ 2) in each cluster category (B = re-experiencing, C = avoidance, D = hyper-arousal), but not meeting criteria for full PTSD, as determined by the Clinician-Administered PTSD Scale [CAPS], (Blake et al., 1998).

2.3. Study drug

Paroxetine was obtained from Andrx Corporation (Davie, Florida) and over-encapsulation and matching placebo identical in appearance was provided by Fisher (Allentown, PA). Study drug was dispensed at each study visit (except screening and final study visits), with flexible dosing as dictated by patient compliance with study medication, one paroxetine patient discontinued due to scheduling conflicts - data at 5 weeks carried forward for these two patients). Mean age for placebo group was 35.86 years (± 9.69 S.D.); mean age for paroxetine group was 39.21 (± 4.70 S.D.).3 Mean final dose in paroxetine group = 34 mg/day, range 30–40 mg/day.

3. Results

2.3. Side effect profiles in patients randomized to paroxetine or placebo

Paroxetine was generally well-tolerated in OEF/OIF era veterans.5 No serious adverse events occurred during this study in either group.

4. Discussion

This pilot RCT with paroxetine is the first to report results from a pharmacological intervention in subthreshold PTSD. Although changes in PTSD symptoms were not significantly different in the group receiving paroxetine compared to the placebo group (see Table 1). Mean SPRINT scores improved non-significantly by 43.2% in the paroxetine group (mean change = 3.8 points) compared to 21.9% in the placebo group (mean change = 2.0 points). Mean total HADS scores improved by 30.4% following treatment with paroxetine (mean total HADS score change = 3.40 points) compared to improvement in HADS scores by 1.7% following treatment with placebo (mean total HADS score change = 0.17 points), unpaired Student’s t-test of change scores, P < 0.005.4

3.3. Side effect profiles in patients randomized to paroxetine and placebo

Paroxetine was generally well-tolerated in OEF/OIF era veterans.5 No serious adverse events occurred during this study in either group.
possibility that intervention with a pharmacological agent may reduce symptoms associated with subthreshold PTSD. Importantly, paroxetine was generally well-tolerated in this OEF/OIF era cohort of veterans with subthreshold PTSD. Initial results are promising, demonstrate feasibility, and potentially contribute to a foundation for future hypothesis-testing.

The main limitation of this pilot RCT is very small sample size, and these results will clearly require replication in a larger cohort to determine if preliminary clinical signals are observable in larger investigations. Additionally, results should be interpreted with caution since there was no change in the primary outcome measure (PTSD symptoms as assessed by the CAPS), and since multiple secondary outcome measures were examined (increasing the likelihood of Type I error, as there were no corrections for multiple comparisons in this exploratory pilot RCT). There were also no women among the 12 participants who completed 5 or more weeks of the study, potentially affecting generalizability. Mean CAPS scores in the group randomized to paroxetine were also quite low at baseline, and hence modifications to study entry criteria for future investigations may be warranted to target a population with a greater degree of subthreshold PTSD symptoms (so that clinical change post-intervention could potentially be detected more easily if present). Although results are very preliminary, initial findings exhibit promise and merit additional study.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.psychres.2012.11.008.

References


