ORIGINAL RESEARCH

Key Words: Trauma, antidepressants, combat, serotonin, norepinephrine

Duloxetine in Military Posttraumatic Stress Disorder

By Gerardo Villarreal, José M. Cañive, Lawrence A. Calais, Gregory Toney, Ashley K. Smith

ABSTRACT ~ *The objective of this prospective study was to assess the efficacy and tolerability of duloxetine in the treatment of in military veterans with posttraumatic stress disorder (PTSD). Twenty subjects were enrolled in this 12-week, open-label trial. Diagnosis and symptom severity were assessed with the Clinician Administered PTSD Scale (CAPS). Depressive symptoms were assessed the Hamilton Depression Rating Scale. All subjects had a CAPS score of at least 60 at baseline. Subjects with lifetime history of psychotic disorders or bipolar illness were excluded. Fifteen participants completed 12 weeks of treatment, five dropped-out from the trial, 3 due to side effects. For patients who discontinued, missing values were estimated using "the last observation carried forward" method. Significant improvements were seen on: CAPS total and all subscales, depression and sleep measures. Most of the improvement was observed by week 2 of treatment. Nine participants (45%) were classified as responders, defined by 20% or greater improvement on CAPS total score. The mean daily dose of duloxetine was 81 mg. The most common side effects were constipation (20%) diarrhea (25%) and nausea (20%). Two subjects developed tachycardia, one withdrew from the trial due to this problem. Duloxetine had a fast onset of action and was effective in about half of the subjects, it was well tolerated in most subjects. These preliminary results in a difficult to treat population warrant the conduction of a double blind, placebo-controlled study of duloxetine in PTSD.* Psychopharmacology Bulletin. *2010;43(3):26–34.*

INTRODUCTION

Posttraumatic Stress Disorder (PTSD) is characterized by 3 symptom clusters that develop after a traumatic experience: Re-experiencing of the traumatic event,

Drs. Villarreal, MD, Cañive, MD, Behavioral Health Care Line, New Mexico VA Health Care System, Albuquerque, NM; Department of Psychiatry, University of New Mexico School of Medicine, Albuquerque, NM. Mr. Calais, RN, CCRC, Staff Nurse, New Mexico VA Health Care System, Albuquerque, NM. Dr. Toney, PharmD, Behavioral Health Care Line, New Mexico VA Health Care System, Albuquerque, NM. Ms. Smith, BS, Department of Psychology, University of Colorado, Boulder, CO.

To whom correspondence should be addressed: Dr. Gerardo Villarreal, MD, New Mexico VA Health Care System (116A), 1501 San Pedro SE, Albuquerque, NM 87108. Phone: (505) 265-1711 ext. 2133; Fax: (505) 256-5474; E-mail: gerardo.villarreal@va.gov

avoidance of stimuli related to the trauma/numbing of emotional responsiveness and hyperarousal symptoms. Posttraumatic Stress Disorder (PTSD) is common in the general population[1] and has even higher prevalence rates among combat veterans.[2,3] Furthermore, PTSD tends to be chronic and disabling.[4,5]

Treatment guidelines for PTSD recommend the selective serotonin reuptake inhibitor (SSRI) antidepressants as the first line of treatment.[6] Currently, only sertraline and paroxetine have Food and Drug Administration (FDA) approval for the treatment of PTSD.[6] Many chronic PTSD patients, especially male combat veterans, have a partial or minimal response to antidepressants.[7–13] Other agents have also been investigated in the treatment of military PTSD, but the response has been less than optimal.[14,15] This underscores the need to investigate new pharmacotherapies for this condition.

Posttraumatic stress disorder is theorized to involve abnormalities in serotonin, norepinephine and dopamine neurotransmitter systems, among others.[16] Unlike SSRIs, duloxetine has potent and balanced dual reuptake inhibition of both serotonin and norepinephrine.[17,18] Studies in civilians indicated efficacy of the dual serotonin/norepinephrine re-uptake inhibitor (SNRI) venlafaxine in the treatment of PTSD.[19,20] There is also evidence that mirtazapine, an antidepressant with indirect effects on both serotonin and norepinephrine, is effective in PTSD.[21,22] Duloxetine is a novel antidepressant FDA approved for the treatment of major depression, generalized anxiety disorder, fibromyalgia and neuropathic pain. One prior naturalistic study suggested effectiveness of duloxetine in veterans with treatment-refractory PTSD with comorbid major depression.[23] The purpose of this study was to investigate the efficacy and tolerability of duloxetine in the treatment of military PTSD. Secondary outcome measures were levels of depression, sleep quality and chronic pain. We conducted a twelve-week, open-label, flexible dose trial of duloxetine monotherapy in military veterans with PTSD.

MATERIALS AND METHODS

Patients

Subjects were recruited from the Raymond G. Murphy VA Medical Center in Albuquerque, New Mexico. All participants signed a VA R&D Committee and University of New Mexico Institutional Review Board-approved consent. Twenty male veterans with military PTSD and a score of at least 60 on the Clinician-Administered PTSD Scale (CAPS-SX,[24,25]) were recruited. Participants had not taken psychiatric medications within one week prior to the baseline visit (two weeks for

fluoxetine or MAO inhibitors). Other medications were stable for at least one month prior to the baseline visit.

Exclusionary criteria included: 1) Alcohol or drug abuse or dependence within three months of study entry; 2) Lifetime diagnosis of bipolar disorder, or a psychotic disorder; 3) Actively seeking compensation for the effects of the trauma; 4) Initiation or change in evidence-based psychotherapy within 3 months of study entry.

Methods

Clinical variables: PTSD diagnoses and comorbidity were established using (CAPS)[24,25] and the Structured Clinical Interview for DSM-IV with Psychotic Screen[26] respectively. The primary efficacy variable was the total score on the CAPS. Additional secondary assessments included the CAPS symptom cluster subscores; the Clinical Global Impressions Scale-Severity of Illness (CGI-S), the Clinical Global Impressions Scale for Improvement (CGI-I), and the Hamilton Depression Rating Scale (HAM-D). The following self-report questionnaires and scales were also included: The Davidson Trauma Scale (DTS);[27] the Pittsburgh Sleep Quality Inventory (PSQI),[28] the Arizona Sexual Experiences Scale (ASEX)[29] and a Visual Analog Scale (VAS) to assess pain.

Medication: Duloxetine dose was initiated at 30 mg per day and increased up to 120 mg per day by week 8 if ineffective and tolerated. At end of study, duloxetine dose was tapered off by 30 mg every 3 days. Lorazepam up to 3 mg daily was allowed for acute agitation, anxiety or insomnia during the first 2 weeks of treatment.

Data Analysis: The overall analysis across the 6 measurement times for the primary and secondary endpoints was a Repeated Measures (RM) ANOVA. Baseline values were compared to the 12-week visit for completers. Missing values due to dropouts were estimated using the last observation carried forward (LOCF) method. To compare significant changes over time, paired t-test were used as post hoc tests to determine this time course. This analysis was generalized to handle occasional missing values by using SAS's PROC MIXED. Bonferroni corrections were made to protect against Type I errors caused by multiple comparisons. In addition, response to duloxetine was defined as a 20% or greater reduction in the CAPS Total score.

RESULTS

Eighty percent of participants had combat-related PTSD. Demographic characteristics of the sample are presented in Table 1.

TABLE 1

DEMOGRAPHIC CHARACTERISTICS OF SAMPLE (n = 20)

CHARACTERISTIC	MEAN	SD
Age	53.45	11.34
Gender	N	%
Male	18	90
Female	2	10
Race		
Caucasian	8	40
Hispanic/Native American	10	50
African-American	2	10
Type of Trauma		
Combat-Related	16	80
Military Sexual Trauma	1	5
Non-combat	3	15
Comorbid Psychiatric Diagnoses		
Major Depressive Disorder	10	50
Dysthymic Disorder	3	15
Depression NOS	2	10
Panic Disorder	1	5
Alcohol Abuse/Dependence in Remission	15	75
Substance Abuse/Dependence in Remission	3	15
Era Served		
Korea	1	5
Vietnam	11	55
Gulf War (Desert Storm)	5	25
Iraq (OIF/OEF)	2	10
Balkans (Kosovo)	1	5

Fifteen subjects completed the 12 week study with five subjects withdrawn from the protocol prior to the week 12 final visit.

Efficacy: RM ANOVA showed significant improvement between baseline and final visits for: CAPS-Total and all CAPS sub-scale scores (Table 2, Figure 1 and 2), CGI-Severity, HAM-D ($p = 0.005$), DTS ($p = 0.003$), and PSQI global. Results held when Bonferroni correction was applied except the improvement of the CAPS-RXP and CGI-S (Table 2). Post-hoc analysis showed significant improvements on CAPS-Total score between baseline and week 2. No significant differences were observed after week 2 although scores remained stable (see Figure 2). Nine subjects (45%) were rated as responders. One subject achieved remission of PTSD symptoms (CAPS-Total < 20), 2 had final CAPS totals of ≤ 26. CGI-I scores of the 15 completers were: 4 = very much improved, 4 = much improved, 6 = minimally improved, 1 = minimally worse. Of the five participants who withdrew from the study, one had a

TABLE 2

CHANGES IN CLINICAL VARIABLES FOR ENTIRE SAMPLE FROM BASELINE TO FINAL VISIT INCLUDING LAST OBSERVATION CARRIED FORWARD (LOCF), n = 20

VARIABLE	BASELINE MEAN (SE)	ENDPOINT MEAN (SE)	SIGNIFICANCE
CAPS			
RXP	21.50(1.53)	14.95(2.01)	0.008**
AVD	32.00(2.21)	25.90(2.61)	0.004**[a]
HYP	26.55(0.90)	20.15(1.77)	<0.001**[b]
Total	80.05(3.53)	61.00(5.78)	0.001**[b]
CGI Severity	4.70(0.11)	4.10(0.24)	0.019*
HAM-D	18.30(1.17)	14.53(1.51)	0.005**[a]
DTS	92.05(4.87)	67.65(7.60)	0.003**[a]
PSI Global	15.60(0.71)	11.50(0.87)	<0.001**[b]
Visual Analog Scale for Pain (mm)	68.00(4.22)	58.45(5.61)	0.101

CAPS, clinician-administered PTSD scale; RXP, CAPS reexperiencing subscale; AVD, CAPS avoidance/numbing subscale; HYP, CAPS hyperarousal subscale; HAM-D, Hamilton Depression Rating Scale; DTS, Davidson Trauma Scale; PSI, Pittsburgh Sleep Index. RM ANOVA **$p \leq 0.01$, *$p \leq 0.05$.
[a]Retains significance at $p \leq 0.05$ with Bonferroni correction.
[b]Retains significance at $p \leq 0.01$ with Bonferroni correction.

CGI-I of much improved, two had a CGI-I of minimally improved, one had a CGI-I of no change, and one had a CGI-I of minimally worse.

Total daily dose of duloxetine ranged from 30 mg to 120 mg with a mean dose of 81 mg (SD 27.7). There was no difference in the overall level of pain measured with the visual analog scale between the baseline visit and the last evaluation.

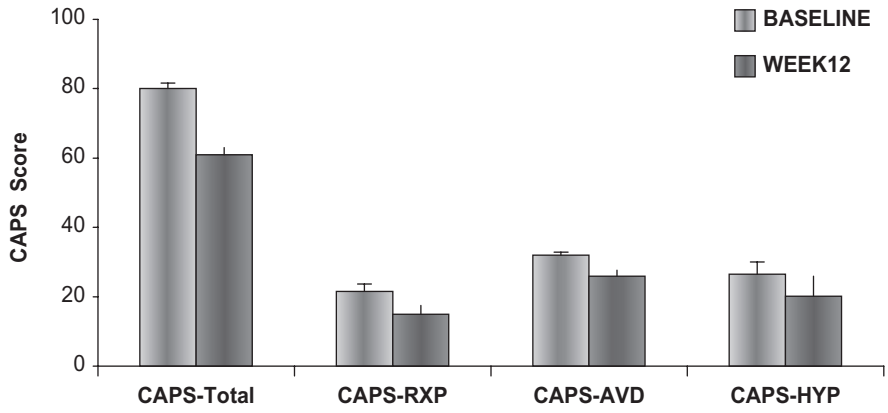
Tolerability and Safety: Five subjects did not complete 12 weeks of treatment. Three participants withdrew consent due to side effects: Tachycardia (1), emesis and vertigo (1) and restlessness (1). One subject withdrew consent due to personal reasons and another was terminated from the trial by the investigators due to emerging paranoia even though he felt his PTSD was improving.

One subject developed tachycardia (max. HR = 131 bpm) on 60 mg that resolved with decreasing the dose to 30 mg and was able to complete the trail.

No significant changes in vital signs, weight, or sexual function (as measured by the ASEX scale) between baseline and final visit were observed. Most common side effects were GI related (anorexia = 15%, constipation = 20%, dry mouth = 15%, diarrhea = 25%, nausea = 20%) and lightheadedness/dizziness = 15%. Adverse events were generally transient and mild to moderate intensity. One patient reported loss of libido lasting throughout the study.

FIGURE 1

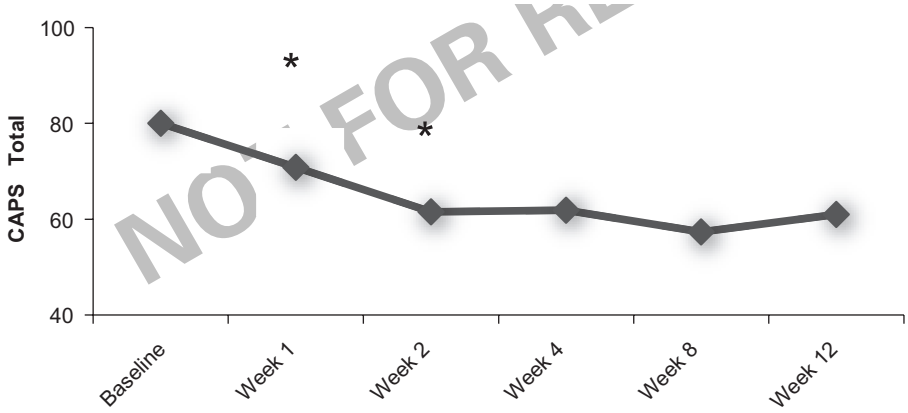
CAPS SCORES BASELINE AND WEEK 12



CAPS-RXP = CAPS re-experiencing subscale; CAPS-AVD = CAPS avoidance/numbness subscale; CAPS-HYP = CAPS hyperarousal subscale.

FIGURE 2

CAPS TOTAL SCORES ACROSS STUDY VISITS



*Significant change from previous visit.

DISCUSSION

Overall conclusions of this trial in military PTSD include that Duloxetine exhibited a positive effect on all three PTSD symptom clusters: Re-experiencing, avoidance/numbing and hyperarousal. Interestingly, most of the improvement in PTSD symptoms occurred by the end of week 2 and was maintained throughout the 12-week study. This finding suggests that duloxetine may have a faster onset of

action on PTSD symptoms than other agents and may imply a mechanism of action different from its presumed antidepressant effect. Some aspects of PTSD (intrusion and hyperarousal symptoms) are theorized to be the result of stress-induced increases in noradrenergic activity.[30] Therefore it is possible that the inhibition of noradrenaline uptake conferred a faster mechanism to duloxetine compared to the SSRI's. However this faster effect was not noticed in a PTSD clinical trial with venlafaxine, another SNRI.[20] In that study, venlafaxine was superior to placebo in terms of CAPS scores only by week 4, with maximal differences at week 12.[20] A study in Korean veterans with mirtazapine, an agent with indirect serotonin and norepinephrine effects, found that compared to sertraline, at week 2 more patients on mirtazapine were rated as responders, however, this difference was only significant by week 6.[22]

Duloxetine was also effective in treating symptoms of depression and sleep quality, even though participants did not find it sedating. Furthermore, duloxetine was well tolerated, side effects were uncommon and mild with only three subjects discontinuing treatment due to adverse events. One subject experienced loss of libido, however, as a group there were no differences in sexual function as measured with the ASEX. Two subjects experienced significant tachycardia which prompted withdrawal from the study in one subject and a dose decrease in another. Tachycardia is mentioned as a rare side effect in the package insert (0.01 to 0.001%), but we found a was much higher rate (20%); we speculate that PTSD subjects may be more sensitive to this noradrenergic effect. This should be monitored in future studies. One participant experienced worsening paranoia (ideas of being poisoned) and was terminated from the trial. His PTSD was improving and he was tolerating the medication well. In retrospect, we suspect he already had these delusions at baseline but hid them during the initial interview; therefore the psychotic symptoms were not considered to be an effect of duloxetine. Although PTSD exacerbation has been reported with duloxetine,[31] we did not observe that effect.

A surprising finding in this cohort of subjects was the lack of benefit in chronic pain. We obtained a general measure of pain level with a visual analog scale but did not focus specifically on neuropathic pain, the FDA-approved use of this drug.

The outcome of this open-label trial in military-related PTSD, a more treatment refractory population, suggests that duloxetine is effective and well tolerated. Our results with duloxetine are promising but should be taken with caution due to the open label nature of the study. A double-blind, placebo-controlled trial of duloxetine in PTSD seems warranted. Our finding of faster onset of action awaits replication. ✤

ACKNOWLEDGMENTS

This study was supported by an investigator-initiated grant from Elli-Lilly to Dr. Cañive and was presented at the College of Psychiatric and Neurologic Pharmacists (CPNP), Jacksonville, FL, April 20, 2009 and the New Clinical Drug Evaluation Unit (NCDEU), Hollywood FL, June 29–July 2, 2009.

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