A Randomized, Placebo-Controlled Trial of Mirtazapine for the Treatment of Posttraumatic Stress Disorder in Veterans

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ABSTRACT

Objective: The aim of this study was to determine the efficacy of mirtazapine, a tetracyclic antidepressant, as monotherapy for the treatment of posttraumatic stress disorder (PTSD).

Methods: This multisite, randomized, double-blind, placebo-controlled trial was conducted between April 2006 and November 2010 at the Tuscaloosa and Birmingham Veterans Affairs Medical Centers in Alabama. US military veterans who met *DSM-IV* criteria for PTSD were randomly assigned to placebo (n = 39) or mirtazapine (n = 39) titrated up to 45 mg/d for an 8-week double-blind period followed by an 8-week open-label phase of mirtazapine treatment. The primary outcome efficacy measure was the Structured Interview for Posttraumatic Stress Disorder (SIP). Secondary measures included other measures of PTSD, depression, and sleep. Analyses of treatment groups involved mixed-model procedures using a random intercept to test the hypotheses that mirtazapine would be more effective than placebo in reducing symptoms of PTSD and depression and improving quality of sleep.

Results: Seventy-eight participants were randomized with 61 completing the 8-week controlled phase and 48 completing the open-label phase. No significant differences were observed between groups on the primary outcome of SIP scores during the controlled phase ($P = .418$). In secondary outcomes, significant improvements per the Clinical Global Impressions–Improvement scale were found for the mirtazapine group compared to the placebo group ($P = .041$). The 8-week open-label phase demonstrated significant symptom improvement in SIP total score ($P = .0003$) and in scores on the SIP re-experiencing ($P = .0007$), avoidance ($P = .0309$), and hyperarousal ($P = .0014$) subscales. There were no significant differences in the occurrence of adverse events between groups.

Conclusions: This study did not show efficacy of mirtazapine monotherapy in the treatment of PTSD. Identification of more effective treatments, either as monotherapy or adjunctive, for PTSD is imperative.

Trial Registration: ClinicalTrials.gov identifier: NCT00302107

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Posttraumatic stress disorder (PTSD) is characterized by a distressing emotional, behavioral, and physiologic reaction that follows a witnessed or experienced traumatic event. Descriptions of "traumatic hysteria" and "shell shock" have evolved over a century through several variations of diagnostic criteria for PTSD,[1] culminating in the 5th edition of the *Diagnostic and Statistical Manual of Mental Disorders*[2] (*DSM-5*), which increased the number of symptom clusters from 3 (re-experiencing, avoidance, and hyperarousal clusters) to 4 (intrusive re-experiencing, avoidance behaviors, negative alterations in cognition and mood, and hypervigilance and reactivity clusters). The cross-national lifetime prevalence of PTSD is 3.9% of the total and 5.6% of the trauma-exposed population, with higher prevalence in women, high-income countries, and survivors of sexual assault.[3] PTSD occurs in approximately 23% of Operations Enduring Freedom and Iraqi Freedom (OEF/OIF) veterans.[4] Major depressive, substance use, and anxiety disorders co-occur with PTSD in up to 50% of the cases.[5] A hallmark of PTSD is sleep disturbance, including distressing nightmares, which may affect the efficacy of first-line treatments and indicate a need for a targeted sleep-enhancing medication, such as mirtazapine.[6,7]

Among many complex biological correlates, PTSD is associated with central nervous system noradrenergic and serotonergic (5-HT) disruptions that contribute to dysfunctional threat detection, fear learning, emotional regulation, and contextual processing.[8,9] Pharmacologic interventions that target noradrenergic and/or 5-HT neurotransmissions, such as mirtazapine, may offer therapeutic relief to patients recovering from PTSD.[10]

A variety of pharmacologic therapies have been studied for the treatment of PTSD; however, the only medications currently approved by the US Food and Drug Administration (FDA) for the treatment of PTSD are the selective serotonin reuptake inhibitors (SSRIs) sertraline and paroxetine. Although the most recent clinical practice guidelines[11] recommend SSRIs and the serotonin-norepinephrine reuptake inhibitor venlafaxine as first- and second-line medication treatment for PTSD, clinical trials have not shown consistent benefit of SSRIs for veterans with PTSD.[12–14] The United Kingdom's guidelines for pharmacologic treatment of PTSD[15] concluded that

Clinical Points

- Identifying effective pharmacologic treatments for chronic posttraumatic stress disorder (PTSD) in military veterans has been difficult over the past 4 decades; however, mirtazapine has a unique pharmacologic mechanism of action and showed promising results in earlier pilot studies.
- Although mirtazapine is better in improving overall clinical status in US military veterans, it is no better than placebo in specifically improving PTSD, depression, or sleep.
- Mirtazapine is well tolerated and does not exhibit more side effects than placebo.

paroxetine, mirtazapine, amitriptyline, and phenelzine were medications that had evidence of efficacy. The limited gap in effective pharmacotherapies for treatment of PTSD in military and veteran populations makes investigation of other medications a priority.

Mirtazapine is a tetracyclic antidepressant that is FDA-approved for the treatment of major depressive disorder. Mirtazapine has also shown positive improvement in patients with comorbid substance use disorders, anxiety, and agitation.[16] It has a unique mechanism of action that makes it appealing as a potential treatment option for PTSD. Mirtazapine enhances both noradrenergic and 5-HT transmission via α_2-autoreceptor and α_2-heteroreceptor antagonism and acts as an antagonist at the 5-HT_2 and 5-HT_3 receptors, allowing selective 5-HT_{1A} neurotransmission.[17] Sustained treatment with mirtazapine results in a 75% increase in the firing rate of 5-HT and a 30% increase in the firing rate of noradrenergic neurons.[18] Mirtazapine provides anxiolytic and antidepressant effects while avoiding the unwanted side effects commonly seen with SSRIs such as insomnia, sexual dysfunction, and nausea.[16]

Four open-label and 3 controlled trials suggest that mirtazapine is beneficial in the treatment of PTSD,[19–25] with an effect size of 0.27 (95% confidence interval [CI], −1.08 to 0.54).[22,26] However, most of these studies were limited by small sample size, selective outcome reporting, and open-label design. In retrospective reviews of electronic medical records, Bernardy and colleagues[27] found that 10% of veterans with PTSD were prescribed mirtazapine, and Kim and fellow researchers[28] found mirtazapine to be the preferred antidepressant in veterans with PTSD who had a higher risk for poorer outcomes, concurrent substance abuse, or multiple medical conditions. With the aim to further test the efficacy of mirtazapine, we conducted a multisite, randomized, placebo-controlled trial of mirtazapine for the treatment of PTSD. Following the double-blind phase, participants continued in an 8-week open-label phase to provide additional symptom and tolerability outcomes. This study is unique in that mirtazapine was used as monotherapy and it was conducted in a US military veteran sample.

METHODS

This study was an 8-week prospective, randomized, double-blind, placebo-controlled trial followed by an 8-week open-label phase conducted at the Tuscaloosa Veterans Affairs Medical Center (TVAMC) and the Birmingham Veterans Affairs Medical Center (BVAMC) in Alabama between April 2006 and November 2010. This study was registered at www.clinicaltrials.gov (identifier: NCT00302107). It was approved by the TVAMC and BVAMC institutional review boards and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. Voluntary and written informed consent was obtained from all participants prior to their taking part in the research.

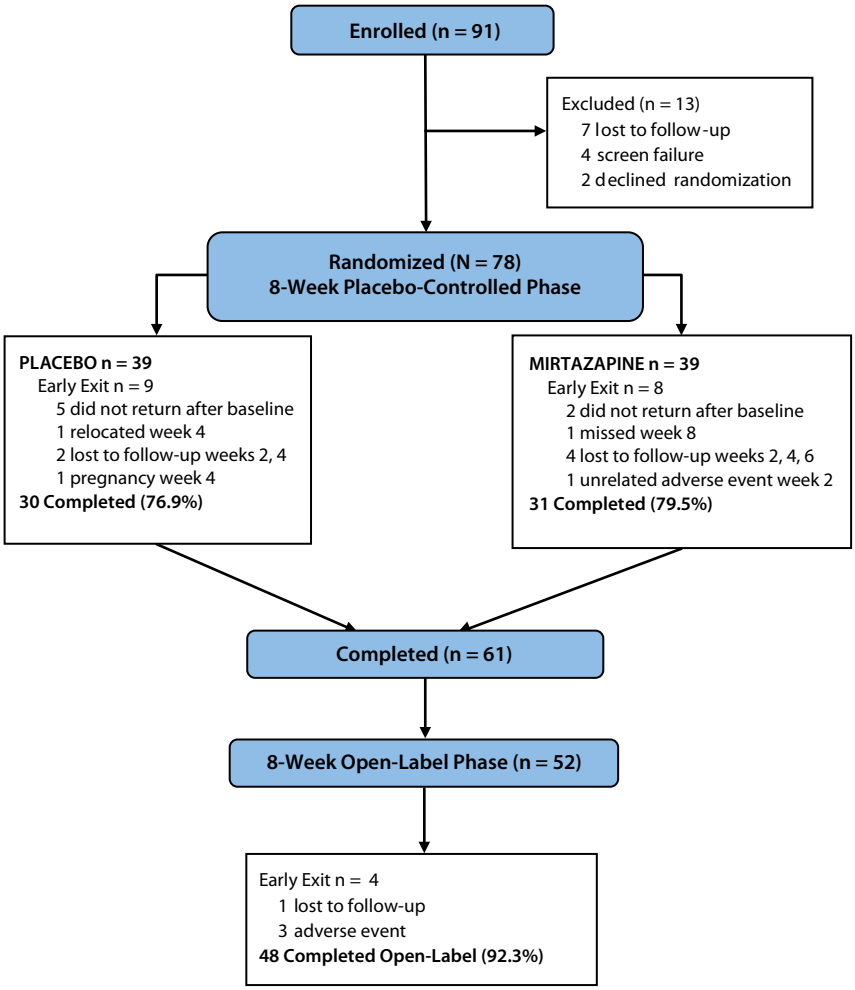
Subjects

Participants were recruited from VA mental health or PTSD clinics, typically as a new consult or self-referral. No community or media advertisements were used to recruit participants. Male and female US military veterans of any race or ethnicity were eligible for inclusion, if all of the following criteria were met: 19–65 years of age, current PTSD diagnosis (based on *DSM-IV* criteria confirmed by the Mini-International Neuropsychiatric Interview (MINI)[29] and the Clinician Administered PTSD Scale–Diagnosis for *DSM-IV* (CAPS),[30] baseline total CAPS score of ≥ 45, no substance abuse or dependence for the previous 4 weeks (other than nicotine and caffeine), free of psychotropic medications for the previous 2 weeks (4 weeks for fluoxetine), and clinically stable medical examination and laboratory tests. Participants were excluded if 1 of the following criteria was met: lifetime history of bipolar I, psychotic, and cognitive disorders; active suicidal, homicidal, or psychotic ideation; history of sensitivity to mirtazapine; unstable general medical conditions that would contraindicate the use of mirtazapine; or score of ≥ 6 on question 10 (suicidal thoughts) on the Montgomery-Asberg Depression Rating Scale (MADRS). Women of childbearing potential had to use a medically approved method of birth control during the study and were excluded if pregnant, breastfeeding, or planning to become pregnant or breastfeed during the study.

Study Drug

Participants meeting eligibility criteria were randomized in a 1:1 double-blind fashion to receive either overencapsulated mirtazapine or a look-alike placebo. Participants were initiated on one capsule of 15-mg mirtazapine or placebo at bedtime, which was increased by one 15-mg mirtazapine or placebo capsule each week as tolerated to a maximum of 45 mg mirtazapine or placebo (ie, 3 capsules) per day. The minimum target dose was 30 mg per day. Compliance was assessed by pill counts at the follow-up visits. At the end of the 8-week double-blind period, the participants entered an 8-week open-label phase of mirtazapine titrated as tolerated to 45 mg at bedtime.

Figure 1. CONSORT Diagram for the Trial of Mirtazapine in Veterans With Posttraumatic Stress Disorder



The participants and investigators remained blinded as to the allocation status during the placebo-controlled phase. Except for low-dose sedative-hypnotics, used sparingly for insomnia (ie, trazodone, lorazepam, or temazepam), no other psychotropic medication or concurrent evidence-based psychotherapy was allowed during the study period. Use of the sleep rescue medication was tracked in the VA pharmacy records and the concomitant medication assessment at each visit.

Assessments

The primary outcome efficacy measure was the Structured Interview for Posttraumatic Stress Disorder (SIP),[31] which is a 17-item clinician-administered rating scale for PTSD based on *DSM-IV* criteria. The SIP has excellent test-retest reliability (0.89; $P = .00001$), internal consistency (Cronbach α of 0.80), and correlation with the Davidson Trauma Scale (DTS; $r = 0.67$, $P = .0001$)[32] and the Impact of Event Scale ($r = 0.49$ $P = .0001$).[33] The investigators included the CAPS as an independent measurement for baseline eligibility so that the pressure to enroll participants did not bias the scoring of the SIP primary outcome measurement; ie, assessments for eligibility may be biased toward baseline score inflation and contribute to placebo response and thus disrupt drug-to-placebo signal detection.[34,35] However, the investigators administered the CAPS on a monthly basis to provide a means to compare this study to previously published results.

The secondary outcome efficacy measures included the CAPS for symptoms for the past week (CAPS-SX), DTS,[31] MADRS,[36,37] Clinical Global Impressions–Severity of Illness scale (CGI-S) and CGI-Improvement scale (CGI-I),[38] Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q),[39] Pittsburgh Sleep Quality Index (PSQI),[40] and Sheehan Disability Scale (SDS).[41] As much as possible, each participant was evaluated by the same clinical rater throughout the study. Data on most outcome measures were collected every 2 weeks. In consideration of minimizing participant burden, the CAPS-SX was scheduled monthly.

Adverse events (AEs) were recorded as they were spontaneously reported to clinical questions; ie, no structured review of potential AEs was conducted. Weight was measured systematically at study visits, and an AE

Table 1. Baseline Demographics and Clinical Characteristics of the Randomized Sample[a]

Variable	Mirtazapine (n = 39)	Placebo (n = 39)	Total (N = 78)
Sex			
Male	37 (94.9)	36 (92.3)	73 (93.6)
Female	2 (5.1)	3 (7.7)	5 (6.4)
Race			
White	11 (28.2)	19 (48.7)	30 (38.5)
Black	26 (66.7)	20 (51.3)	46 (59.0)
Other	2 (5.1)	0 (0)	2 (2.6)
Spanish, Hispanic, or Latino	1 (2.6)	0 (0)	1 (1.3)
Marital status			
Married	20 (51.3)	23 (59.0)	43 (55.1)
Divorced/separated	10 (25.6)	10 (25.6)	20 (25.6)
Single	8 (20.5)	6 (15.4)	14 (17.9)
Widowed	1 (2.6)	0 (0)	1 (1.3)
Education			
Less than high school	1 (2.6)	0 (0)	1 (1.3)
High school diploma/equivalent	13 (33.3)	13 (33.3)	26 (33.3)
Some college	19 (48.7)	18 (46.2)	37 (47.4)
Technical or associate	4 (10.3)	5 (12.8)	9 (11.5)
College or higher	2 (5.1)	3 (7.7)	5 (6.4)
Branch of service			
Army	25 (64.1)	18 (46.2)	43 (55.1)
National Guard	9 (23.1)	13 (33.3)	22 (28.2)
Marine Corps	3 (7.7)	4 (10.3)	7 (9.0)
Navy/Air Force/other	2 (5.1)	4 (10.3)	6 (7.7)
Employment			
Employed	27 (69.2)	31 (79.5)	58 (74.4)
Unemployed	8 (20.5)	4 (10.3)	12 (15.4)
Retired	2 (5.1)	0 (0)	2 (2.6)
Disabled	2 (5.1)	4 (10.3)	6 (7.7)
VA service–connected disability			
Receiving	22 (56.4)	16 (41.0)	38 (48.7)
Filing or appealing	6 (15.4)	7 (17.9)	13 (16.7)
Not receiving or filing	11 (28.2)	15 (38.5)	26 (33.3)
Missing	0 (0)	1 (2.6)	1 (1.3)
Concurrent mental disorders (current)			
Major depressive disorder	22 (56.4)	24 (61.5)	46 (59.0)
Panic	9 (23.1)	7 (17.9)	16 (20.5)
Agoraphobia	9 (23.1)	11 (28.2)	20 (25.6)
Social anxiety	8 (20.5)	4 (10.3)	12 (15.4)
Alcohol dependence (past year)	4 (10.3)	4 (10.3)	8 (10.3)
Alcohol abuse (past year)	7 (17.9)	5 (12.8)	12 (15.4)
Substance dependence (past year)	3 (7.7)	0 (0)	3 (3.8)
Substance abuse (past year)	0 (0)	1 (2.6)	1 (1.3)
Length of combat service, mean (SD), mo	16.6 (13.7)	16.8 (22.6)	16.5 (17.7)
Length of PTSD, mean (SD), mo	52.7 (44.2)	58.8 (70.7)	55.8 (58.6)
Age, mean (SD), y	37.7 (10.3)	38.1 (9.5)	38.0 (9.9)
Age range, y	22–56	22–55	22–56

[a]Values are shown as n (%) unless otherwise noted.
Abbreviations: PTSD = posttraumatic stress disorder, VA = Veterans Administration.

for "weight gain" was recorded based on actual weight and a complaint by the participant.

Statistical Analyses

The 2 treatment groups were compared for baseline differences in demographics, clinical characteristics, and severity scores for each outcome measure. These analyses used *t* tests for continuous data, χ^2 tests for categorical data, and Wilcoxon procedures for any variable not having an underlying normal distribution. There were no significant imbalances in any baseline variables between the 2 groups. Thus, an adjusted analysis was not done for any endpoint in the data analysis. In an intent-to-treat analysis, the mirtazapine and placebo groups were compared using mixed-model random slope analysis, with group, time, and group-by-time interaction terms. The a priori primary efficacy outcome was defined as the change in the SIP severity score from baseline to week 8 (ie, last visit of the double-blind phase). The model consisted of 2 factors: treatment at 2 levels and time, and group-by-time interaction. In keeping with the published literature, "response" was defined as ≥ 30% reduction in CAPS-SX and CGI-S scores ≤ 2 (1 = very much improved, 2 = much improved), and groups were compared using the Fisher exact test. All randomized subjects who took at least 1 dose of the study medication were included in the safety analysis.

RESULTS

Ninety-one veterans signed informed consent, and 78 participants were randomized and were included in the analysis. The CONSORT diagram (Figure 1) provides the count and reasons for those who were not randomized (n = 13) and those who did not return after baseline or exited early. Sixty-one participants completed the 8-week placebo-controlled phase of the study (78.2% retention). Twenty-five participants from the mirtazapine arm and 27 from the placebo are (n = 52 total) entered the open-label phase, and, of these, 48 (92.3%) completed the additional 8-week open-label phase of the study.

As shown in Table 1, of the randomized participants, 94% were male, 63% were minority race, and the age range was 22 to 56 years with a mean ± SD age of 38.0 ± 9.9 years. The mean ± SD duration of PTSD illness was 55.8 ± 58.6 months, or 4.65 ± 4.9 years. Concurrent psychiatric conditions included major depressive disorder (59%), panic disorder (20.5%), agoraphobia (25.6%), and other diagnoses shown in Table 1. All but 3 participants had experienced combat-related trauma as the primary cause of PTSD.

As shown in Table 2 and Figure 2, there were no significant differences between the placebo and treatment groups for the primary outcome SIP scores (total, SIP-B, SIP-C, or SIP-D). The between-group Cohen *d* effect size for the SIP total score change from baseline to week 8 is 0.2 (small effect). Very few participants showed worsening in PTSD symptoms (4 in each group had an increase of ≥ 5 points in SIP total scores). There were no significant between-group differences for CAPS total scores or CAPS PTSD clusters (CAPS-B, CAPS-C, CAPS-D), MADRS scores, CGI-S scores, DTS scores, or PSQI scores. The Q-LES-Q and SDS did not show significant differences between groups. However, the change in CGI-I scores between weeks 2 and 8 was significantly greater for the mirtazapine compared to the placebo group ($P = .041$); 8 mirtazapine-treated participants but only 3 placebo-treated participants were "much" or "very much" improved at week 6 or 8. Four participants treated with mirtazapine met the strict definition of response

Table 2. Primary and Secondary Outcomes for Mirtazapine Versus Placebo in the Treatment of PTSD[a]

Rating Scale[b]	Baseline (n = 78)	Week 2 (n = 69)	Week 4 (n = 63)	Week 6 (n = 59)	Week 8 (n = 61)	*P* Value	Week 8 Change From Baseline
SIP total score						.418	
Mirtazapine	38.2 (7.1)	33.7 (9.8)	33.8 (10.7)	33.2 (10.6)	32.1 (11.4)		−7.6 (9.9)
Placebo	39.2 (8.4)	35.9 (10.6)	35.3 (10.2)	32.4 (10.0)	33.2 (10.2)		−5.8 (7.4)
SIP-B						.263	
Mirtazapine	11.0 (2.7)	9.2 (3.1)	9.0 (4.2)	9.0 (3.6)	8.1 (3.7)		−3.5 (3.5)
Placebo	11.4 (3.2)	10.1 (4.0)	10.0 (3.5)	8.7 (3.9)	9.7 (3.6)		−1.8 (3.0)
SIP-C						.613	
Mirtazapine	14.7 (4.2)	13.3 (4.6)	14.0 (4.8)	13.4 (5.1)	13.1 (5.6)		−2.1 (4.4)
Placebo	15.2 (4.5)	14.1 (4.9)	13.7 (5.0)	12.9 (4.9)	13.1 (5.0)		−1.9 (4.2)
SIP-D						.488	
Mirtazapine	12.5 (2.1)	11.1 (3.5)	10.7 (3.2)	10.8 (3.1)	10.9 (3.5)		−2.0 (3.4)
Placebo	12.6 (2.2)	11.6 (3.5)	11.6 (3.2)	10.8 (2.7)	10.4 (3.3)		−2.1 (2.9)
CAPS total score						.304	
Mirtazapine	79.1 (13.9)	…	71.4 (20.4)	…	67.6 (23.1)		−14.4 (15.5)
Placebo	82.9 (16.4)	…	73.9 (22.8)	…	70.8 (22.9)		−12.5 (14.2)
CAPS-B						.236	
Mirtazapine	21.4 (6.0)	…	18.7 (8.1)	…	16.5 (7.5)		−6.0 (6.4)
Placebo	22.9 (6.1)	…	19.9 (8.3)	…	19.0 (7.7)		−4.1 (5.2)
CAPS-C						.543	
Mirtazapine	30.7 (7.9)	…	29.5 (8.9)	…	27.7 (11.6)		−3.9 (7.8)
Placebo	32.3 (8.6)	…	29.1 (11.1)	…	28.2 (11.2)		−4.3 (7.5)
CAPS-D						.357	
Mirtazapine	27.0 (4.3)	…	23.3 (6.6)	…	23.3 (6.8)		−4.5 (5.6)
Placebo	27.7 (4.5)	…	24.9 (7.6)	…	23.5 (6.4)		−4.1 (5.0)
MADRS total score						.555	
Mirtazapine	26.5 (7.3)	23.2 (7.7)	20.1 (7.7)	19.3 (7.7)	20.3 (8.8)		−6.7 (8.7)
Placebo	26.5 (8.1)	23.8 (8.2)	23.6 (9.5)	21.1 (10.1)	21.0 (8.3)		−5.6 (8.9)
CGI-S score						.127	
Mirtazapine	4.7 (0.6)	4.5 (0.8)	4.4 (0.8)	4.3 (0.8)	4.2 (1.1)		−0.5 (0.9)
Placebo	4.8 (0.7)	4.8 (0.7)	4.7 (0.8)	4.5 (0.7)	4.5 (0.8)		−0.3 (0.6)
CGI-I score						.041	
Mirtazapine	…	3.6 (0.6)	3.1 (0.8)	3.0 (0.8)	2.9 (0.8)		−0.7 (0.9)
Placebo	…	3.8 (0.5)	3.5 (0.6)	3.3 (0.7)	3.2 (0.6)		−0.5 (0.7)
DTS score						.647	
Mirtazapine	83.9 (20.6)	78.4 (27.2)	79.2 (30.9)	81.8 (27.5)	75.0 (29.3)		−12.9 (20.9)
Placebo	84.0 (24.8)	83.7 (24.9)	82.0 (27.6)	78.2 (30.7)	75.3 (31.4)		−12.1 (24.2)
PSQI score						.414	
Mirtazapine	15.6 (4.1)	15.4 (4.8)	15.0 (5.8)	14.7 (4.9)	13.9 (4.9)		−2.7 (4.3)
Placebo	16.6 (4.1)	15.9 (5.3)	15.5 (5.8)	13.3 (4.9)	12.9 (4.9)		−3.7 (4.2)

[a]Values are shown as mean (SD).
[b]For all rating scales, lower score is better.
Abbreviations: CAPS = Clinician Administered PTSD Scale, CAPS-B = CAPS score for criterion B re-experiencing symptoms, CAPS-C = CAPS score for criterion C avoidant symptoms, CAPS-D = CAPS score for criterion D hyperarousal symptoms, CGI-I = Clinical Global Impressions–Improvement scale, CGI-S = Clinical Global Impressions–Severity of Illness scale, DTS = Davidson Trauma Scale, MADRS = Montgomery-Asberg Depression Rating Scale, PSQI = Pittsburgh Sleep Quality Index, SIP = Structured Interview for Posttraumatic Stress Disorder, SIP-B = SIP score for criterion B re-experiencing symptoms, SIP-C = SIP score for criterion C avoidant symptoms, SIP-D = SIP score for criterion D hyperarousal symptoms.

compared to none of the participants on placebo ($P = .1128$). There were no differences between groups (19 mirtazapine, 18 placebo) in terms of showing a clinically meaningful response, defined as a decrease in CAPS total score of ≥ 10 points.

As shown in Table 3, symptoms were significantly improved in the open-label mirtazapine phase per the overall SIP and SIP subscales, CAPS total and subscales, CGI-S, CGI-I, and MADRS, but not the PSQI.

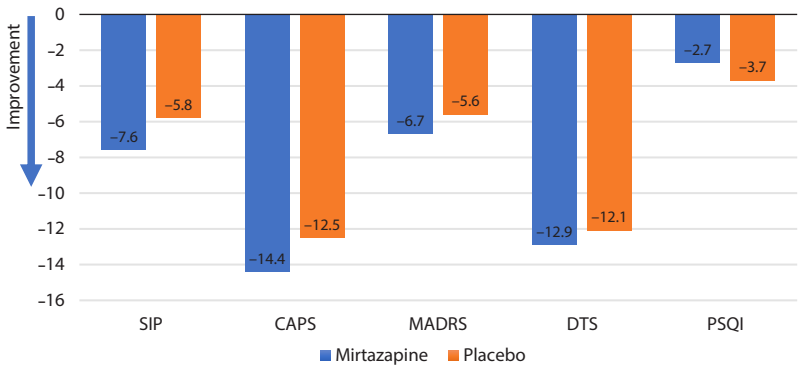
Study Medication Dosing

For the group assigned to mirtazapine, the mean ± SD daily dose after titration was 38.5 ± 10.5 mg. There was a significant difference in the number of participants that needed an intermittent sleep rescue medication during the double-blind phase: 11 participants in the placebo group (28.2%) and 3 participants in the mirtazapine group (7.7%) required rescue sleep medication ($P = .018$). Of the participants in the placebo arm, 5 were prescribed temazepam, 3 were prescribed trazodone, and 3 were prescribed lorazepam; and in the mirtazapine arm, 2 were prescribed temazepam and 1 was prescribed lorazepam. During the open-label phase, the mean ± SD daily dose of mirtazapine after titration was 40.6 ± 9.4 mg.

Adverse Events

There were no significant differences in the occurrence of adverse events between treatment groups. During the double-blind period, 4 patients on placebo had unrelated adverse events (ie, viral gastroenteritis, allergy to insect repellent, steroid-induced panic, and opiate-induced sedation). Three patients on mirtazapine treatment had

Figure 2. Week 8 Mean Change From Baseline in PTSD, Depression, and Sleep Outcomes



Abbreviations: CAPS = Clinician Administered PTSD Scale, DTS = Davidson Trauma Scale, MADRS = Montgomery-Asberg Depression Rating Scale, PSQI = Pittsburgh Sleep Quality Index, PTSD = posttraumatic stress disorder, SIP = Structured Interview for Posttraumatic Stress Disorder.

Table 3. Primary and Secondary Outcomes for Open-Label Phase of Mirtazapine for PTSD[a]

Rating Scale[b]	Week 8 Mean (SD)	Week 16 Mean (SD)	Change From Week 8 to Week 16	*P* Value
SIP total	32.7 (10.8)	27.6 (12.0)	−5.1 (9.0)	.0003
SIP-B	8.9 (3.7)	6.8 (4.5)	−2.0 (3.9)	.0007
SIP-C	13.1 (5.2)	12.0 (5.6)	−1.2 (3.8)	.0309
SIP-D	10.7 (3.4)	8.8 (3.7)	−1.8 (3.7)	.0014
CGI-S	4.3 (1.0)	3.7 (1.1)	−0.7 (0.9)	.0001
CGI-I	3.1 (0.8)	2.3 (1.3)	−0.8 (1.3)	.0001
DTS	75.1 (30.1)	71.2 (33.3)	−3.1 (16.3)	.2002
MADRS	20.7 (8.5)	16.2 (9.5)	−4.1 (8.8)	.0020
PSQI	13.4 (4.9)	11.8 (5.2)	−1.2 (3.7)	.0649
CAPS total	69.2 (22.3)	56.2 (26.3)	−10.8 (19.0)	.0004
CAPS-B	17.8 (7.7)	14.0 (9.3)	−3.5 (7.9)	.0043
CAPS-C	28.0 (11.1)	25.2 (11.7)	−3.0 (8.2)	.0175
CAPS-D	23.4 (6.4)	18.7 (7.2)	−4.3 (7.3)	.0002

[a]Values are shown as mean (SD).
[b]For all rating scales, lower score is better.
Abbreviations: CAPS = Clinician Administered PTSD Scale, CAPS-B = CAPS score for criterion B re-experiencing symptoms, CAPS-C = CAPS score for criterion C avoidant symptoms, CAPS-D = CAPS score for criterion D hyperarousal symptoms, CGI-I = Clinical Global Impressions–Improvement scale, CGI-S = Clinical Global Impressions–Severity of Illness scale, DTS = Davidson Trauma Scale, MADRS = Montgomery-Asberg Depression Rating Scale, PSQI = Pittsburgh Sleep Quality Index, SIP = Structured Interview for Posttraumatic Stress Disorder, SIP-B = SIP score for criterion B re-experiencing symptoms, SIP-C = SIP score for criterion C avoidant symptoms, SIP-D = SIP score for criterion D hyperarousal symptoms.

unrelated adverse events during the double-blind period (ie, shortness of breath secondary to history of granulomas, stiffness and foot pain secondary to fibromyalgia, and pulled muscle with cracked rib secondary to sneezing episode). One participant in the mirtazapine group and 1 participant in the placebo group experienced a severe adverse event (ie, hospitalizations for preexisting medical conditions).

Adverse events that might be related to study medication during the double-blind period in the placebo group included the following: 8 reported weight gain (no dose change), 3 had drowsiness (1 lowered dose), 2 reported sleep-related disturbances (lowered dose), 1 had loss of consciousness with fall and fracture (no dose change), 1 had increased appetite (no dose change), and 1 reported dizziness and headache (decreased dose). No participant on placebo stopped the study medication. For those in the mirtazapine group, 9 experienced weight gain (no dose change), 3 had sleep disturbances/vivid dreams (no dose change), 2 had increased sedation (decreased dose), 2 had decreased concentration with 1 also having decreased reflexes (1 decreased dose and 1 discontinued study medication), 2 had headache (1 decreased dose), and 2 had combination of sedation and headache (no dose change). Only 1 participant on mirtazapine treatment stopped the medication due to the adverse event of decreased concentration.

During the open-label phase, 2 reported sedation (1 decreased dose and 1 discontinued medication), 1 reported nocturnal hot flash (decreased dose), 1 had nightmares and aggression (dose decrease), 1 experienced weight gain (decreased dose), 1 had dizziness (discontinued medication), 1 had irritability and perceptual disturbances (discontinued medication), and 1 complained of sedation, vivid dreams, perceptual disturbances, and increased appetite (discontinued medication). In total, 4 participants (7.7%) in the open-label phase discontinued the medication due to adverse events, 3 of whom dropped out of the study early.

DISCUSSION

In this sample of predominantly male combat veterans, mirtazapine monotherapy did not significantly differ from placebo in the treatment of PTSD on primary or secondary outcome measures, except that mirtazapine held an advantage over placebo in overall global clinical improvement. Although our findings stand in contrast to those of other studies that suggest mirtazapine may be beneficial in the treatment of PTSD. However, those previously published studies were not an adequate test of efficacy due to the lack of placebo control, small sample size, selective reporting of outcomes, lack of double-blinding, and use of last-observation-carried-forward analyses.

Most previously published studies of mirtazapine were noncontrolled and open-label[19–21,24]; however, 1 study[23] was an open randomized comparison to sertraline, and 2 studies[22,25] were double-blind, randomized, placebo-controlled studies. In the 6-week study by Chung and colleagues,[23] 100 Korean military veterans diagnosed with PTSD were openly randomized to mirtazapine or sertraline monotherapy, and both medications were found to be effective in reducing PTSD measures, with no differences between groups. There were a significantly greater number of responders in the mirtazapine group (88%) compared to the sertraline group (69%; $P = .039$). The mirtazapine group had more severe baseline CAPS scores (mean ± SD = 103.2 ± 24.4) compared to sertraline group (88.8 ± 23.9), as well as baseline scores shown in our study sample (79.1 ± 13.9). The limitations of Chung and colleagues' study[23] were its open-label design and lack of placebo arm, which contribute to rater and participant biases.

Davidson and colleagues[22] randomized participants (14% veterans; 50% women) to mirtazapine or placebo (2:1 ratio) and used data from the 26 participants who returned for at least one post-randomization visit. The early dropout rate was 31%. The response rates were significantly greater in the mirtazapine group (65%) than in the placebo group (22%; $P = .04$), although there were no group differences in the primary PTSD outcome score from baseline to week 8. Mirtazapine yielded significantly greater improvement on the secondary SIP and the Hospital Anxiety Scale, while difference on the DTS failed to reach significance. For the mirtazapine group, the mean ± SD SIP score went from 34.7 ± 7.0 at baseline to 17.4 ± 4 at week 8, and for the placebo group, the SIP score went from 38.4 ± 6.7 at baseline to 32.9 ± 12.7 at week 8 ($P = .04$). The baseline SIP scores were comparable to the baseline scores observed in our study. Between-group effect sizes were 0.49 to 1.06 for the PTSD measures and 1.14 for the Hospital Anxiety Scale. Using Cochrane bias assessment rules, Lee and colleagues[14] determined that study to have high bias risk and calculated a nonsignificant pre-/posttreatment between-group difference in effect size for primary PTSD outcome to be −0.81 (95% CI, −1.65 to 0.02).

In a 24-week randomized, double-blind trial (n = 36), Schneier and colleagues[25] found that the combination of sertraline and mirtazapine significantly enhanced rates of remission for the sertraline plus mirtazapine group (39%) compared to mirtazapine plus placebo (11%; $P = .042$) and reduced depressive symptoms ($P = .023$), but there were no significant differences between treatment groups in the primary outcome for PTSD (CAPS) or for secondary outcomes for sleep or quality of life. The effect size for the CAPS outcomes was medium ($d = 0.51$; 95% CI, 1.23 to −0.22). The small sample size and substantial dropout rate (76%) are major limitations; however, the use of a master's/doctoral-level independent assessor who was blinded to medication and adverse events is a strength of the study. The demographics of the study sample were very different from those in our study, ie, younger age, 64% female, 61% Hispanic, and 100% noncombat trauma. The results of this study suggest that mirtazapine in combination with sertraline is worthy of additional clinical research.

This treatment study is not the first to fail to show efficacy in a sample of predominantly male military veterans with PTSD. Other examples include studies of sertraline,[13] prazosin,[42] risperidone,[43] and trauma-focused psychotherapy.[44] In addition, it is not uncommon to fail to confirm or reproduce findings from open-label or small placebo-controlled studies. As pointed out by Kapur and Munafò[45] and Leon and colleagues,[46] smaller studies produce imprecise estimates of effect and/or false positives combined with the fact that negative studies are often not published and positive studies are not always replicated, so a true estimate of effects is often not available prior to launching a multisite placebo-controlled study. Another factor that may have contributed to the null finding is the difficulty in recruiting highly symptomatic patients into a placebo-controlled study of a treatment that is already widely available, thereby representing a sample in lower overall distress.

Mirtazapine has potential side effects that can be particularly worrisome in patients recovering from PTSD, including increased irritability, anxiety, and startle response.[47] Although not significantly different from those in the placebo group, the most bothersome side effects from mirtazapine in our sample of combat veterans were daytime sedation, unusually vivid nightmares, and irritability. These side effects may have contributed to the null findings. Although used sparingly, the rescue sleep medication may have diminished our ability to detect differences in the sleep scale (PSQI); ie, rescue medication was used significantly more often in the placebo group (28%) than in the mirtazapine group (8%).

In conclusion, this study did not support the efficacy of mirtazapine in the treatment of PTSD in US military veterans. The strengths of this study include the randomized, double-blind, placebo-controlled, monotherapy design. The limitations are the modest sample size, length of study (8 vs 12 weeks), use of rescue sleep medication, and the homogeneity of the study sample (ie, limiting the generalizability of these findings to civilians or females). Our results do not rule out the possibility of mirtazapine as an effective adjunctive treatment to other psychotropic medications or psychotherapy in the treatment of PTSD. Identifying the best path of treatment for PTSD has proven to be difficult, yet it remains an essential and imperative task for researchers.

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