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Impact of Traumatic Stress on Sleep and Management Options in Women

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SYNOPSIS

Following exposure to traumatic stress, women are at greater risk than men for developing symptoms of some psychiatric disorders including insomnia and nightmares. Sleep disturbance is one of the most refractory symptoms of posttraumatic stress disorder (PTSD). Patients often experience residual sleep-related symptoms after completing cognitive behavioral therapies (CBT) for PTSD. Although several studies examined efficacy of psychological or pharmacological interventions for trauma-related sleep disturbances, a limited number focused on women. Those studies demonstrated preliminary evidence for efficacy of CBT for insomnia, imagery rehearsal therapy, and combinations of these techniques in treating insomnia and nightmares in trauma-exposed women. Prazosin as an adjunct to other psychotropic medications and/or psychotherapy is a potentially efficacious strategy for treating nightmares in trauma-exposed women.

Keywords

trauma; posttraumatic stress disorder; women; insomnia; nightmares; pharmacotherapy; cognitive behavioral therapy; imagery rehearsal therapy

INTRODUCTION

Insomnia, including trouble falling and staying asleep, is one of the most commonly reported symptoms following trauma exposure.^{1,2} These symptoms are often persistent and may affect trauma survivors long-term, even for several decades.³ Following exposure to a traumatic event, women are at greater risk than men for developing symptoms of psychiatric disorders including posttraumatic stress disorder (PTSD), depression, and anxiety disorders.^{4,5} Insomnia and recurrent nightmares about trauma are symptoms of some of these

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disorders.⁶ Women and adolescent girls are more likely than men and boys to report insomnia and nightmares in the general population^{7–10} and also after trauma exposure.^{11–13} Therefore, it is particularly important for women to be properly assessed and treated for sleep disturbances following trauma. Although women face unique sleep challenges following trauma, treatment studies focusing on trauma-related sleep disturbances in women are limited. The purpose of this paper is to briefly review findings from studies about sleep disturbances in trauma-exposed women. We then focus on psychotherapy and pharmacotherapy clinical trials examining efficacy for treating sleep-related symptoms in trauma-exposed women and suggest areas for further research.

SUBJECTIVE AND OBJECTIVE SLEEP CHANGES IN TRAUMA-EXPOSED WOMEN

A large proportion of trauma-exposed women suffer from insomnia and/or trauma-related nightmares. Sleep disturbance is particularly pronounced in women with PTSD, the diagnostic criteria for which include insomnia and recurrent trauma nightmares along with other symptoms such as intrusive trauma memories, hyperarousal, and avoidance of trauma reminders.⁶ In a sample of female Vietnam veterans, 73% veterans with PTSD and 62% of those without PTSD endorsed trouble initiating sleep; 91% of veterans with PTSD versus 59% without PTSD reported trouble maintaining sleep.¹⁴ In male Vietnam veterans, 44% of veterans with PTSD and 6% of those without PTSD reported trouble initiating sleep, and 91% with PTSD versus 63% without PTSD endorsed trouble maintaining sleep.¹⁵ Female veterans may be more vulnerable to sleep onset insomnia compared to male counterparts. Nightmares were reported by 73% of female rape victims with PTSD and by 27% of those without PTSD four weeks after rape, and persisting nightmares were experienced at 12 week post-rape especially in victims with PTSD (reported by 63% of victims with PTSD and by 12% of victims without PTSD).²

Despite significant sleep disturbances reported by trauma-exposed individuals, in both genders, trauma- or PTSD-related objective sleep alterations are subtle and often observed in measures of sleep depth (i.e., amount of light N1 stage of sleep and deep slow wave sleep) or rapid-eye-movement sleep.^{16,17} Lipinska and colleagues examined effects of PTSD and trauma exposure on subjectively and objectively measured sleep by comparing female sexual assault survivors with and without PTSD and non-trauma-exposed controls.¹⁷ Their analysis of laboratory polysomnographic sleep revealed that trauma exposure was associated with decreased deep sleep (N3 slow wave sleep) and that PTSD was related to increased light sleep (N1 sleep stage). However, they did not find any other trauma- or PTSD-related objective sleep alterations.

Perceived safety of the laboratory sleep environment has been suggested as a potential explanation for the discrepancy between laboratory polysomnography and self-report survey findings in trauma-exposed individuals.¹⁸ Consistent with this hypothesis, female sexual assault survivors, particularly those with PTSD, in the aforementioned study by Lipinska and colleagues¹⁷ reported perceiving the laboratory sleep environment as quieter, safer, and more comfortable than home. Individuals with PTSD endorsed worse subjective sleep

quality compared to the other groups in the home, but this group difference was not found in the laboratory setting.¹⁷ In addition, an actigraphy-study captured longer sleep onset latency and lower sleep efficiency in women exposed to mixed-types of trauma with PTSD compared with women without PTSD, suggesting sleep initiation and maintenance difficulties in the home sleep environment in women with PTSD.¹⁹

It has been suggested that people who experienced trauma in situations associated with sleep (e.g., in a bedroom, darkness) are vulnerable to sleep disturbances as they are likely to experience heightened vigilance in sleep environments and perform sleep-interfering safety behaviors such as checking locks multiple times or leaving lights on.²⁰ Women are more likely than men to be exposed to traumatic events that often occur in sleep-related situations and carry increased risk for persistent psychological disturbances, such as sexual violence, childhood sexual abuse, and intimate partner violence.^{4,21,22} It is important that clinicians assess possible associations between the trauma context and sleep-interfering behaviors while planning insomnia treatment strategies for women.

COGNITIVE BEHAVIORAL STRATEGIES

Sleep disturbance has been considered one of the most refractory symptoms of PTSD.^{23,24} Cognitive behavioral therapies (CBTs) for PTSD, including cognitive processing therapy (CPT) and prolonged exposure (PE), are evidence-based treatments for PTSD and reduce symptoms of insomnia, but patients often report clinically significant residual sleep symptoms after completing the treatment. Zayfert and DeViva²⁴ found that in 27 civilian participants (89% female) who achieved remission of overall PTSD after CBT for PTSD, nearly half of participants continued to report residual insomnia. In two studies of female sexual assault survivors with PTSD,^{23,25} both sleep quality and insomnia symptoms improved after CPT or PE; however, overall subjective sleep disturbance remained at clinical levels post-treatment. Table 1 lists findings of these and other studies of psychological treatments for trauma-related sleep disturbances that included female participants.

One of the most utilized evidence-based treatments for insomnia is CBT for insomnia (CBT-I). CBT-I is multimodal treatment, typically lasting between 6–8 sessions, that includes sleep hygiene education, sleep restriction, stimulus control, sleep compression, relaxation, and cognitive therapy.²⁶ Stimulus control works through the extinction of a conditioned arousal in bed and bedroom by breaking associations between a person's bed/bedroom and wakefulness and strengthening associations of the bed/bedroom with sleep. To promote the ability to relax and fall asleep in bed, patients are instructed to use their bed only for sleep and sexual activities and leave their bedroom when they are not able to fall asleep. In the sleep restriction technique, the amount of time a person spends in bed is initially reduced in order to build up pressure for sleep, leading to the reduction of unwanted wakefulness throughout the night.²⁶ The cognitive therapy module primarily focuses on cognitive restructuring of dysfunctional, overly-held beliefs about sleep. Cognitive restructuring often relies on a combination of two techniques. One technique, commonly called “thought-stopping,” includes recognizing the occurrence of dysfunctional thoughts about sleep and implementing cognitive and/or behavioral strategies to stop the thought. The other technique, often called “challenging automatic thoughts,” involves developing alternative

thoughts to dysfunctional automatic thoughts. For example, a dysfunctional belief about sleep such as, “Insomnia is ruining my ability to enjoy life and prevents me from doing what I want,” may increase distress and arousal pre-sleep, thus interfering with sleep. By challenging automatic thoughts, such a belief may be adjusted to a more helpful, balanced thought like, “I have been able to enjoy my day occasionally and accomplish some things I want, even on days when I slept poorly. I would like to sleep better to function better during the day.”

CBT-I has a large body of research supporting its efficacy. In Morin and colleagues’²⁷ review of 37 psychological insomnia treatment studies, five of CBT-I individual modules met criteria for empirically-supported treatments for insomnia: stimulus control therapy, relaxation, paradoxical intention, sleep restriction, and cognitive-behavioral therapy. The most recent meta-analysis of 14 randomized controlled trials (RCTs) of CBT-I for primary insomnia²⁸ reported medium to large effect sizes for between-treatment-and-control-group ($d = 0.24 - 1.09$) and within-subject effects ($d = 0.67 - 1.09$) on indices of sleep initiation and maintenance.

Although the efficacy of CBT-I has also been studied in individuals with insomnia and comorbid PTSD, only a small number of studies included a significant proportion of female participants. Two RCTs of CBT-I have been conducted with individuals (approximately 70% female) with PTSD (see Table 1).^{29,30} One of the RCTs conducted by Wagley and colleagues²⁹ revealed significant therapeutic effects on sleep outcomes only in the analysis of within-subject changes, but not in the analysis of between-group differences.

Recently, brief behavioral therapy for insomnia (BBT-I), a 1- to 4-session treatment comprising only behavioral modules of CBT-I, was developed,³¹ and its efficacy has been demonstrated in various types of insomnia patients, including individuals with trauma-related insomnia.^{32–36} The only BBT-I trial with a large proportion of female (57%) examined effects of a one-session version of BBT-I in a small sample ($N = 7$) of victims of violent crimes with PTSD.³⁶ From baseline to 6-weeks post-treatment, sleep quality significantly improved. While the improvements in diary-measured sleep initiation and maintenance had effect sizes of moderate to large, the changes were not statistically significant probably because of the small sample size. The efficacy of BBT-I has been suggested in controlled trials of trauma-exposed veterans; however, these trials included small proportions (10% – 15%) of women.^{34,35}

Imagery rehearsal therapy (IRT), initially developed to treat nightmares, has been applied to treatment of trauma-related nightmares.^{37,38} IRT normally takes place over three sessions and includes education about the development and function of nightmares, prompting to view recurrent nightmares as habits or learned behaviors, rescripting of nightmares, and then practicing the positive and more comfortable rescripted dream imagery during the daytime. In the largest trial of IRT with only female participants ($N = 168$), sexual assault survivors who received IRT had greater reductions in nightmare frequency and improvement in sleep quality and PTSD symptoms compared to women on a waitlist.³⁸

IRT has also been combined with CBT-I techniques. In a majority female (84%) sample of victims of violent crimes with PTSD, 62 participants completed a 10-hour group treatment combining IRT techniques with CBT-I modules including sleep hygiene, stimulus control, and sleep restriction.³⁹ Participants demonstrated pre- to post-treatment improvements in nightmare frequency, sleep quality, and insomnia. In a study of 22 veterans with PTSD (32% female) IRT was abbreviated and presented as a “dream rescripting” technique in combination with CBT-I.⁴⁰ This combined intervention yielded greater improvement in nightmares and symptoms of insomnia and PTSD compared to usual care. These results suggest that IRT in combination with more traditional CBT-I techniques may deliver relief from trauma-related nightmares, but further research is needed to determine whether the combination of IRT and CBT-I is more effective than IRT alone.

There have been only a few studies on efficacy of cognitive behavioral strategies for sleep disturbance in trauma-exposed women. Studies with female-only or predominantly female samples have showed therapeutic effects of CBT-I, IRT, and combinations of these techniques on sleep quality and insomnia and nightmare severity in trauma-exposed individuals; however, methodological shortcomings such as small sample sizes, within-subject comparisons, and use of waitlist controls limit the conclusiveness of the study findings.

PHARMACOLOGICAL STRATEGIES

A large number of clinical trials have been conducted to examine efficacy of pharmacological treatment for PTSD; however, not many studies report results specific to sleep problems or specific to women. Two selective serotonin reuptake inhibitors (SSRIs), sertraline and paroxetine, are the only medications currently approved for treating PTSD by the U.S. Food and Drug Administration. Although these SSRIs help reduce PTSD symptoms, clinical trials have shown limited efficacy. In RCTs with PTSD patients, only half of the patients treated with sertraline achieved “responder” criteria,^{41,42} and 30% of patients treated with paroxetine achieved remission.⁴³ Effects of SSRIs or other antidepressants on sleep-related PTSD symptoms have been examined in a small number of clinical trials, and none of the trials demonstrated sufficient treatment effects. Moreover, two RCTs with a large proportion of women with PTSD suggested that sertraline may increase the risk of insomnia.^{41,44} Effects of nefazodon, a serotonergic antidepressant, on insomnia symptoms and nightmares were observed only in open label trials (in male only and female only trials).^{45–47} Table 2 summarizes sleep-related findings of pharmacological studies that included trauma-exposed female participants.

Benzodiazepines and other hypnotics are commonly prescribed medications for patients with PTSD, and higher prescription rates of these medications were observed in women with PTSD treated at U.S. Veterans Affairs (VA) compared to male counterparts.^{48,49} However, benzodiazepines have been ineffective in treating or preventing PTSD,⁵⁰ and some treatment guidelines for PTSD recommend against use of benzodiazepines as associated risks such as dependence may outweigh benefits.^{51,52} Further, benzodiazepines may interfere with extinction of conditioned fear, a learning process essential for recovery from PTSD, and compromise the benefit of exposure therapy.^{53,54} Two cross-over design studies with small

samples (6 male veterans, and 6 patients with unspecified gender) have examined effects of benzodiazepines on sleep symptoms in PTSD,^{55,56} but neither study indicated benefit.

Non-benzodiazepine hypnotics such as zolpidem and eszopiclone are among the most commonly prescribed medications for insomnia in the U.S. general population as well as veterans with PTSD.^{49,57} Despite their popularity, evidence for their efficacy in treating sleep symptoms in PTSD is limited. Our literature search yielded only one double-blind RCT indicating potential benefits of non-benzodiazepine hypnotics on trauma-related sleep disturbance. In this small RCT in civilians with PTSD ($N = 24$, 71% female), eszopiclone improved sleep quality and shortened sleep onset latency compared to placebo.⁵⁸ In contrast, in a clinical trial of male combat veterans with PTSD comparing zolpidem and hypnotherapy as an adjunctive treatment to an SSRI, zolpidem was less effective than hypnotherapy in improving sleep quality and decreasing sleep disturbance.⁵⁹

Prazosin, a centrally active $\alpha 1$ -adrenergic receptor antagonist, is the only agent that has demonstrated efficacy in treating PTSD-related sleep symptoms in multiple double-blind RCTs.⁶⁰ In these trials, prazosin was administered adjunctively with stable psychotropic medications and/or psychotherapy. Several RCTs with prazosin that included women (5 – 85%) have shown therapeutic effects for PTSD-related nightmares and insomnia symptoms (see Table 2).^{34,61–63} However, some studies did not find significant therapeutic effects. A recent multicenter VA clinical trial for combat-related sleep disturbance ($N = 304$, 2% female) found that prazosin did not significantly change either nightmares or sleep quality compared to placebo.⁶⁴ Further, Germain and colleagues³⁴ found no differences between prazosin and BBT-I in treating nightmares and insomnia ($N = 50$, 10% female), although both prazosin and BBT-I were superior to placebo (Table 1).

DRUG-ASSISTED PSYCHOTHERAPY

Recently, drug-assisted psychotherapy has begun to gain traction as a strategy to enhance therapeutic effects of psychotherapy for PTSD. We were able to find only one study reporting effects of this approach on sleep symptoms in a sample that included women. D-cycloserine, a partial agonist at the N-methyl-D-aspartate receptor, has been hypothesized to augment effects of exposure therapy by enhancing extinction learning.⁶⁵ In the double-blind RCT of individuals exposed to the 9/11 attacks ($N = 25$, 24% female), d-cycloserine was administered 90 minutes before each exposure therapy session, and participants reported lower insomnia severity at 6-month follow-up compared to placebo.⁶⁵

SUMMARY AND CONCLUSION

Following a traumatic experience, women are more likely than men to experience symptoms of psychiatric disorders, including insomnia and recurrent nightmares. Sleep disturbance is one of the most commonly reported and refractory symptoms of PTSD. However, only a small number of psychological or pharmacological clinical trials have focused on sleep symptoms in trauma-exposed women. SSRIs, currently first-line pharmacological treatments for PTSD, have not demonstrated sufficient evidence for their efficacy in treating trauma-related sleep disturbance. Among multiple pharmacological agents tested, prazosin has the

strongest evidence for improving nightmares and insomnia symptoms in trauma-exposed individuals. Limited evidence suggests that eszopiclone and d-cycloserine-assisted exposure therapy may be effective in treating insomnia symptoms in trauma-exposed individuals, but more studies are needed. CBT for PTSD, a first-line psychological treatment, improved insomnia symptoms; however, patients often experienced residual sleep symptoms. Clinical trials have indicated that certain cognitive behavioral strategies such as CBT-I, IRT, or combinations of these strategies may contribute to the improvement of sleep disturbances in trauma-exposed women. However, further evidence from methodologically strong studies is needed.

It has been increasingly recognized that sleep contributes to the maintenance of mental and physical health.^{66,67} Therefore, properly treating sleep disturbances after trauma is important not only for relieving distress associated with sleep difficulties, but also for promoting health and quality of life of trauma-exposed women.

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KEY POINTS

1. Following exposure to traumatic stress, women are at greater risk than men for developing symptoms of some psychiatric disorders including insomnia and nightmares.
2. Individuals with posttraumatic stress disorder (PTSD) often experience residual sleep disturbance after completing cognitive behavioral therapies for PTSD.
3. Cognitive behavioral therapy for insomnia, imagery rehearsal therapy, and combinations of these techniques are possibly effective in treating insomnia and nightmares in trauma-exposed women.
4. Prazosin as an adjunct to other psychotropic medications or psychotherapy is a potentially efficacious strategy for treating nightmares in trauma-exposed women.

Table 1**Psychotherapy Clinical Trials for Sleep Disturbance in Trauma-Exposed Women**

Citation	Intervention	Sample	Trauma Type	Sleep Outcomes ^a
Studies with an All-Female Sample (k=4)				
Gutner et al. (2013) ²⁵	CPT, PE, or minimal attention	N = 171 100% PTSD	Sexual assault	↓Insomnia ↓Nightmares ↑Subjective sleep quality
Krakow, Hollifield, et al. (2001) ³⁸	IRT or waitlist control	N = 168 95% PTSD	Sexual assault	↓Nightmares ↑Subjective sleep quality
Galovski et al. (2009) ²³	CPT or PE	N = 108 100% PTSD	Sexual assault (childhood or adulthood)	=Subjective sleep quality (between CPT and PE) -For both conditions, pre- to post-treatment changes: ↑Subjective sleep quality ↓Insomnia
Krakow, Sandoval, et al. (2001) ⁶⁸	IRT or no-treatment control	N = 19 Unknown % PTSD	Sexual assault	↓Nightmares =Subjective sleep quality
Studies with a Mixed Gender Sample (k=10)				
Zayfert & DeViva (2004) ²⁴	CBT for PTSD	N = 25 89% Female 100% PTSD	Mixed civilian	-Pre- to post-treatment changes (significance not reported): ↓Insomnia (88% to 48%) ↓Severe insomnia (64% to 30%)
Krakow, Johnston, et al. (2001) ³⁹	CBT-I+IRT	N = 62 84% Female 100% PTSD	Violent crime	-Pre- to post-treatment changes: ↓Nightmares ↑Subjective sleep quality ↓Insomnia
Wagley et al. (2013) ²⁹	2 sessions CBT-I or treatment as usual	N = 30 70% Female 23% PTSD	Mixed civilian	= Subjective sleep quality -Pre-treatment to 4-week follow-up change: ↑Subjective sleep quality
Belleville et al. (2011) ⁶⁹	CBT for PTSD	N = 55 69% Female 100% PTSD	Mixed civilian	-Pre- to post-treatment changes: ↑Subjective sleep quality ↓Subjective sleep latency -Post-treatment to 6-month follow-up changes: ↓Subjective sleep quality ↑Subjective sleep latency
Talbot et al. (2014) ³⁰	CBT-I or waitlist control	N = 45 69% Female 100% PTSD	Mixed civilian and military	↓Diary insomnia symptoms ↑Subjective sleep quality ↓Questionnaire insomnia ↓Nightmares & disruptive nocturnal behaviors ↑Polysomnography total sleep time =Actigraphy wake after sleep onset, total sleep time
Germain et al. (2007) ³⁶	1 session version of BBT-I	N = 7 57% Female 100% PTSD	Violent crime	- Pre- to post-treatment changes: ↑Subjective sleep quality

Citation	Intervention	Sample	Trauma Type	Sleep Outcomes ^a
				=Diary sleep quality =Diary insomnia
Ulmer et al. (2011) ⁴⁰	CBT-I+IRT or treatment as usual	<i>N</i> = 22 32% Female 100% PTSD	Mixed military	↓Diary and questionnaire insomnia ↓Nightmares ↑Subjective sleep quality
Germain et al. (2014) ³⁵	BBT-I or information only control	<i>N</i> = 40 15% Female 30% PTSD	Combat	= Rate of insomnia remission post-treatment ↓Insomnia ↑Subjective sleep quality
Germain et al. (2012) ³⁴	BBT-I, prazosin, or placebo control	<i>N</i> = 50 10% Female 58% PTSD	Mixed military	- BBT-I and prazosin, compared to control: ↓Insomnia =Subjective sleep quality =Sleep disturbances No difference between prazosin and BBT-I
Margolies et al. (2013) ⁷⁰	CBT-I/IRT or waitlist control	<i>N</i> = 37 10% Female 100% PTSD	Mixed military	↓Diary and questionnaire insomnia ↑Subjective sleep quality ↓Nightmares

Note: k = number of studies;

^aThis column indicates findings of comparisons between treatment and control groups unless otherwise specified; CPT = cognitive processing therapy; PE = prolonged exposure; PTSD = posttraumatic stress disorder; IRT = imagery rehearsal therapy; CBT-I = cognitive behavioral therapy for insomnia; BBT-I = brief behavioral therapy for insomnia.

Table 2
Pharmacological Clinical Trials for Sleep Disturbance in Trauma-Exposed Women

Citation	Medication (mg/day)	Design Duration	Sample	Trauma Type	Sleep Outcomes ^d
Selective serotonin reuptake inhibitors; Serotonin and norepinephrine reuptake inhibitors (k = 4)					
Meltzer-Brody et al. (2000) ⁷¹	Fluoxetine (10–60)	RDBPC 12 weeks	N = 53 91% female 100% PTSD	Mixed civilian	= Nightmares ↓ Insomnia (questionnaire) = Insomnia (clinician interview)
Davidson et al. (2001) ⁴⁴	Sertraline ^b (50–100)	RDBPC 12 weeks	N = 208 78% female 100% PTSD	Mixed civilian	= Subjective sleep quality ↑ Insomnia as adverse event (35% vs. 22%)
Brady et al. (2000) ⁴¹	Sertraline ^b (50–200)	RDBPC 12 weeks	N = 187 73% female 100% PTSD	Mixed civilian & combat	↑ Insomnia as adverse event (16% vs. 4%)
Stein et al. (2009) ⁷²	Venlafaxine ER (37.5–300)	Pooled analysis of two RDBPC trials 12 weeks	N = 687 61% female 100% PTSD	Mixed civilian & combat	= Insomnia = Nightmares
Other antidepressants (k = 4)					
McRae et al. (2004) ⁷³	Nefazodone (100–600)	Randomized double-blind comparison to sertraline 12 weeks	N = 26 77% female 100% PTSD	Mixed civilian	↑ Subjective sleep quality pre- to post-treatment. No difference from sertraline.
Davidson et al. (1998) ⁴⁵	Nefazodone (50–600)	Open label 12 weeks	N = 17 76% female 100% PTSD	Mixed civilian	-Pre- to post-treatment changes: ↓ Insomnia ↓ Nightmares
Schneier et al. (2015) ⁷⁴	Mirtazapine adjunct to sertraline ^c (30–45)	RDBPC 24 weeks	N = 36 64% female 100% PTSD	Mixed civilian	= Subjective sleep quality
Becker et al. (2007) ⁷⁵	Bupropion SR ^d (100–300)	RDBPC 8 weeks	N = 30 21% female 100% PTSD	Mixed civilian and military	= Subjective sleep quality
GABA receptor agonist; GABA reuptake inhibitor (k = 3)					

Citation	Medication (mg/day)	Design Duration	Sample	Trauma Type	Sleep Outcomes ^d
Pollack et al. (2011) ⁵⁸	Eszopiclone ^e (3)	RDBPC crossover 3 weeks	N = 24 71% female 100% PTSD	Mixed civilian and military	↑ Subjective sleep quality ↓ Subjective sleep latency
Connor et al. (2006) ⁷⁶	Tiagabine (4–16)	Open-label phase 12 weeks followed by RDBPC phase 12 weeks for only responders to open label treatment	Open label phase: N = 26, 73% female, 100% PTSD RDBPC phase: N = 19	Mixed civilian	-Open-label phase pre- to post- treatment changes: ↑ Subjective sleep quality ↓ Insomnia ↓ Nightmares -RDBPC phase: = Subjective sleep quality ↓ Insomnia
Davidson et al. (2007) ⁷⁷	Tiagabine (4–16)	RDBPC 12 weeks	N = 232 66% female 100% PTSD	Mixed civilian & combat	= Insomnia = Nightmares
Prazosin (k = 7)					
Taylor et al. (2008) ⁷⁸	Prazosin ^d (1–6)	RDBPC crossover 7 weeks	N = 13 85% female 100% PTSD	Mixed civilian	↑ Objective total sleep time ↓ Nightmares ↓ Distressed awakening
Simpson et al. (2015) ⁷⁹	Prazosin ^d (1–8)	RDBPC 6 weeks	N = 30 37% female 100% PTSD & alcohol dependence	Mixed civilian & combat	= Nightmares
Ahmad-panah et al. (2014) ⁶¹	Prazosin ^d (1–15)	RDBPC comparison to hydroxyzine 8 weeks	N = 100 28% female 100% PTSD	Mixed civilian & war-related	-Prazosin and hydroxyzine, compared to placebo: ↑ Subjective sleep quality ↓ Subjective sleep latency -Prazosin compared to the other groups: ↑ Subjective sleep duration ↓ Nightmares
Raskind et al. (2013) ⁶²	Prazosin ^e (1–25)	RDBPC 15 weeks	N = 67 15% female	Combat	↓ Nightmares ↑ Subjective sleep quality

Citation	Medication (mg/day)	Design Duration	Sample	Trauma Type	Sleep Outcomes ^a
			100% PTSD		
Petrakis et al. (2016) ⁸⁰	Prazosin ^e (2–16)	RDBPC 13 weeks	N = 96 6% female 100% PTSD & alcohol dependence	Mixed military	= Nightmares = Insomnia
Raskind et al. (2007) ⁶³	Prazosin ^e (1–15)	RDBPC 8 weeks	N = 40 5% female 100% PTSD	Combat	↓Nightmares ↑Subjective sleep quality
Raskind et al. (2018) ⁶⁴	Prazosin ^e (1–20)	RDBPC 26 weeks	N = 304 2% female 100% PTSD	Combat	= Nightmares = Subjective sleep quality
Drug-assisted psychotherapy (k = 1)					
Difede et al. (2014) ⁶⁵	D-cycloserine ^d (100mg before weekly exposure therapy sessions)	RDBPC 10 weeks	N = 25 24% female 100% PTSD	9/11 World Trade Center attack	↓Insomnia

Note: k = number of studies; RDBPC = randomized double blind placebo controlled;

^aThis column indicates findings of comparisons between treatment and control groups unless otherwise specified;

^bongoing psychotherapy other than CBT was allowed;

^congoing psychotherapy was allowed;

^dongoing stable psychotropic medications were allowed;

^eongoing stable psychotropic medications or psychotherapy were allowed.