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SLEEP DISORDERS (P GEHRMAN, SECTION EDITOR)

Treatment of Sleep Disturbances in Post-Traumatic Stress Disorder: A Review of the Literature

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Abstract Sleep disturbances are among the most commonly endorsed symptoms of post-traumatic stress disorder (PTSD). Treatment modalities that are effective for the waking symptoms of PTSD may have limited efficacy for post-traumatic sleep problems. The aim of this review is to summarize the evidence for empirically supported and/or utilized psychotherapeutic and pharmacological treatments for post-traumatic nightmares and insomnia. While there are few controlled studies of the applicability of general sleep-focused interventions to the management of the sleep disturbances in PTSD, evidence is growing to support several psychotherapeutic and pharmacological treatments. Future investigations should include trials that combine treatments focused on sleep with treatments effective in managing the waking symptoms of PTSD.

Keywords Psychotherapy · Pharmacotherapy · Sleep disturbance · Insomnia · Nightmares · Post-traumatic stress disorder

This article is part of the Topical Collection on *Sleep Disorders*

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Introduction

Sleep disturbance is a core feature of post-traumatic stress disorder (PTSD) and has been called its hallmark symptom [1]. Although insomnia and recurrent nightmares are included in the diagnostic criteria for PTSD, other sleep disturbances, including obstructive sleep apnea (OSA) [2], periodic limb movement disorder (PLMD) [3, 4], and rapid eye movement sleep behavior disorder (RBD) [5], also have been linked to PTSD. Mood disorders, anxiety disorders, and substance use disorders are often comorbid with PTSD [6] and may also affect the clinical course of this disorder, including the associated sleep disturbances.

Sleep mechanisms have been linked to the development and maintenance of PTSD [7]. Insomnia and recurrent nightmares are two of the most common and distressing symptoms of the disorder [8–10], and they generally exacerbate the waking symptoms of PTSD [11, 12]. Despite the significance and high prevalence of these sleep disturbances, studies of the first-line treatments of PTSD, both psychotherapeutic and pharmacological, rarely examine the effectiveness of these therapeutic modalities for PTSD-related sleep symptoms. This is especially problematic given the evidence for clinically significant residual sleep problems during and following PTSD treatment [13•, 14, 15••]. Finally, persistent symptoms of insomnia and recurrent nightmares have the potential to compromise treatment responses to empirically supported PTSD interventions.

The primary aim of this review is to summarize psychotherapeutic and pharmacological interventions for insomnia and recurrent nightmares in PTSD. We first provide a brief background on the phenomenology of the insomnia and recurrent nightmares. It should be noted that we do not use the terms insomnia and nightmares to refer to formal diagnoses included in the Diagnostic and Statistical Manual of Mental

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Disorders (5th ed.; DSM-5) [16] or the International Classification of Sleep Disorders (ICSD) [17]. Rather, "insomnia" refers to the difficulty sleeping that is a Criterion E hyperarousal symptom of PTSD, and "nightmares" refer to the recurrent distressing trauma-related dreams that are a Criterion B reexperiencing symptom of the disorder. We proceed to discuss sleep disorders and mental disorders that may be comorbid with PTSD, and the implications for treating sleep disturbances in PTSD. Finally, we review the different forms of psychotherapy and pharmacotherapy that have shown utility in treating insomnia and recurrent nightmares in PTSD.

Insomnia and PTSD

Approximately 70 % of individuals with PTSD report difficulty in initiating and maintaining sleep [8]. Insomnia in individuals with PTSD has been linked to increased psychiatric comorbidity, including alcohol use and poor health status [18]. Also, recent studies demonstrate that insomnia symptoms predating the trauma may be an important predictor of, or independent risk factor for, the development of PTSD [19, 20•, 21•]. Gehrman and colleagues [20•] found that predeployment insomnia symptoms in members of the military significantly increased the risk of developing PTSD, depression, and anxiety disorders following deployment. Similarly, Wright and colleagues [21•] found that insomnia symptoms at 4 months post-deployment were a significant predictor of PTSD symptoms as well as depression at 12 months post-deployment. Taken together, these studies highlight the importance of assessing and treating insomnia in both individuals at high risk for developing PTSD and in individuals with established PTSD.

Recurrent Nightmares and PTSD

Recurrent trauma-related nightmares are another highly prevalent and distressing feature of PTSD. Research suggests two types of post-traumatic nightmares, symbolic and replicative [22]. Symbolic nightmares contain normal dream content, with distortions, irrational structures, and eidetic images, with some aspect of the trauma being represented symbolically. On the other hand, replicative nightmares, which have been viewed as highly specific to PTSD, seem to replicate part or all of the traumatic event(s); their content is more logical and lacking in the distortions characteristic of normal dreaming [22, 23]. Estimates of the prevalence of a nightmare disturbance in PTSD vary due to differences in methodology, in particular, the criteria and tools used to define and assess nightmares across studies [24]. By self-report, 52 to 96 % of individuals with PTSD endorsed experiencing frequent nightmares [10, 25]. Similar to insomnia, persistent nightmares in the wake of a traumatic event may predict the subsequent development of PTSD and other psychiatric disorders [25–27]. For example, post-traumatic nightmares within 1 month of experiencing a traumatic event predicted greater PTSD symptom severity 6 weeks and 1 year following the event [28, 29].

Recurrent nightmares have been associated with poor overall sleep quality [30, 31], depression, and heightened risk of suicide [32–34]. Sjostrom and colleagues [34] found that nightmare sufferers had a five-fold increase in suicidality even after controlling for psychiatric diagnosis. There has been increased recognition that persistent nightmares, particularly those seen in PTSD, often require targeted treatment interventions [35].

Obstructive Sleep Apnea and PTSD

OSA is characterized by sleep-related decreases (hypopneas) or pauses (apneas) in respiration [17]. OSA estimates in the general population range from 3 to 7 % in men and 2 to 5 % in women [36]. OSA is commonly comorbid with PTSD, as well as other psychiatric [2] and medical disorders [37]. Sharafkhaneh and colleagues [2] found that individuals with OSA compared to a group without this condition had a higher prevalence of PTSD, depression, anxiety, psychosis, and dementia, with the highest comorbidity rates for depression (21.8 %), PTSD (11.9 %), and other anxiety disorders (16.7 %). OSA is particularly prevalent in PTSD and other trauma-exposed populations, with estimates ranging from 40 to 90 % [38–41]. Yesavage and colleagues [42] recently reported that 69 % of Veterans with PTSD had an apnea-hypopnea index (AHI) >10, indicative of at least mild OSA. The causes, consequences, and possible mechanisms of the reported association between OSA and PTSD require further investigation [2, 43], as do the implications for treatment of these two disorders.

Periodic Limb Movement Disorder and PTSD

PLMD is characterized by periodic highly stereotyped limb movements during sleep [17]. These movements, which occur primarily during non-REM sleep, are often associated with partial arousal or awakening [17]. PLMD is estimated to occur in 4 to 11 % of the general adult population [44]; however, its prevalence in individuals with PTSD is higher. Mellman and colleagues [4] found that 33 % of a group with PTSD had periodic limb movements that ranged from 2 to 33 per hour compared to 0 % in the healthy control group. Similarly, Ross and colleagues [45] and Germain and colleagues [46] found an elevated periodic limb movement index in PTSD patients compared to controls. To date, the highest prevalence of

clinically significant periodic limb movements in a PTSD population (76 %) was found in a group of Vietnam War Veterans [3]. The aforementioned studies had small sample sizes, and their findings are limited to combat-related PTSD (i.e., [4, 45]). However, the possibility that PLMD may contribute to the insomnia often endorsed by individuals with PTSD warrants further investigation. It also is important to keep in mind that antidepressant medications used to treat the PTSD symptom complex (see "Pharmacological Treatments for PTSD" below) can increase the incidence of periodic limb movements, and possibly exacerbate insomnia [47].

Rapid Eye Movement Sleep Behavior Disorder and PTSD

RBD is a parasomnia characterized by REM sleep without atonia on polysomnography and the enactment of REM sleep dreams [17]. Approximately 60 % of cases of RBD are idiopathic, although often the harbinger of a neurodegenerative disorder. RBD also can occur secondary to alcohol use and withdrawal and certain psychotropic medications, antidepressants in particular [17]. Although individuals with PTSD often report prominent, sometimes injurious, movement during sleep [8], and although there is much evidence for a fundamental REM sleep abnormality in PTSD [1, 48, 49], there are limited data on any relationship between RBD and PTSD. Husain and colleagues [5] reported that 56 % of a sample of RBD patients had comorbid PTSD. Additional studies are needed in order to better understand the phenomenology and comorbidity of RBD and PTSD. It also is important to keep in mind that antidepressant medications used to treat the PTSD symptom complex (see "Pharmacological Treatments for PTSD" below) can increase the incidence of RBD, and possibly exacerbate insomnia and recurrent nightmares [50].

Psychiatric Comorbidity in PTSD

In the National Comorbidity Survey, approximately 79 % of women and 88 % of men with PTSD had a lifetime diagnosis of at least one other psychiatric disorder [51]. The most prevalent comorbid diagnoses were depressive disorders, anxiety disorders, and substance use disorders [51–53], all of which are characterized by disturbed sleep. However, there are limited data on sleep in individuals with PTSD comorbid with another psychiatric disorder(s). In a national sample, Leskin and colleagues [10] found that PTSD/panic disorder patients, compared to individuals with PTSD alone, had a higher prevalence of nightmare (96 vs. 71 %) and insomnia (100 vs. 80 %) complaints. Further investigation is needed to examine the extent to which sleep disturbance in PTSD is related to trauma exposure or a consequence of comorbid disorders.

Psychotherapeutic Interventions for PTSD

Several psychotherapeutic interventions for PTSD have been developed. The most widely recognized of these are cognitive behavioral therapies (CBT), including prolonged exposure therapy (PE) and cognitive processing therapy (CPT) [54]. Eye movement desensitization and reprocessing (EMDR) has also been recognized as a treatment for PTSD [54]. However, the Institute of Medicine (IOM) recommended exposure therapies as the only evidenced-based treatments for PTSD [55]. Several meta-analyses of the efficacy of psychotherapeutic interventions for PTSD have been published [56–59], but these rarely examined sleep outcomes [60]. The consensus is that there are large initial improvements in overall PTSD symptom severity [57], with greater effect sizes in studies with a higher proportion of women [57, 58], and small effect sizes in studies with mostly Veterans [57, 58]. There were no significant differences between active psychotherapies [59].

Some studies have considered the effectiveness of psychotherapy for PTSD in managing the associated insomnia and recurrent nightmares [61–65]. For the purposes of the current review, it is important to note that these sleep disturbances were frequently residual complaints following otherwise successful PTSD treatment [61]. Zayfert and DeViva [62] examined 27 patients from a rural tertiary care medical center who no longer met criteria for a PTSD diagnosis following CBT for PTSD. They found that 48 % of subjects reported residual insomnia, without persisting nightmares. Two small studies of flooding (arguably a variation of exposure therapy) in Veterans, neither of which focused on sleep and used validated sleep measures, had conflicting results [63, 64].

In one controlled EMDR study (N=36) that used an unvalidated nightmare measure and no insomnia measure, the nightmare disturbance improved following treatment [65]. Raboni and colleagues [66] found, in a small uncontrolled study, that, following treatment with EMDR, seven patients with PTSD exhibited an increase in sleep efficiency and a reduction in wake time after sleep onset; however, these findings may be the result of habituation over three nights as the first night PSG was used as a baseline measure. Galovski and colleagues [14] found that both PE and CPT were effective in reducing global sleep disturbance in adult female rape survivors; however, sleep impairment remained clinically significant in both groups despite an overall improvement in PTSD symptoms. Recently, Gutner and colleagues [15••] examined the long-term effects of CPT and PE on sleep disturbance. Similar to previous studies [14, 62], they found

significant improvements in waking PTSD symptoms but no remission of the sleep disturbance.

Taken together, the aforementioned studies indicate that existing treatments for PTSD are less effective in ameliorating the sleep disturbance than they are in treating the waking symptoms. Most studies were limited by small sample size, failure to use validated sleep measures, and lack of a control group. Thus, further investigation is required.

Cognitive Behavioral Treatment for Insomnia (CBT-I) in PTSD

To date, few studies have examined the efficacy of psychotherapeutic interventions for insomnia in individuals with PTSD. Cognitive behavioral therapy for insomnia (CBT-I) is a brief intervention aimed at improving overall sleep quality [67, 68]. It includes instruction in stimulus control and sleep restriction, cognitive restructuring, sleep hygiene education, and relaxation training [68]. Stimulus control is designed to limit negative associations with the bed and the bedroom [69]. Sleep restriction training aims to increase sleep drive and sleep efficiency by first limiting the amount of time spent in bed and then gradually increasing this time [69]. Cognitive restructuring identifies and challenges inaccurate beliefs and thoughts that directly interfere with sleep [69]. Sleep hygiene education discourages behaviors, such as alcohol consumption before bed, that interfere with healthy sleep [69]. Relaxation training, including progressive muscle relaxation, breathing exercises, and guided imagery, is designed to reduce the physical and/or mental tension that can delay sleep onset [69].

There is some evidence that CBT-I is efficacious for insomnia related to PTSD. DeViva and colleagues [70] studied five patients who responded to CBT for PTSD but continued to endorse insomnia symptoms. CBT-I was associated with a modest improvement in four of the five patients [70]. In another uncontrolled study of CBT-I in patients with PTSD (N= 8), Gellis and Gehrman [71•] found significant improvements in self-reported sleep quality and the insomnia severity index (ISI) score, but no change in actigraphically measured sleep. Recently, Talbot and colleagues [72••] conducted the first randomized clinical trial of an 8-week course of CBT-I, provided individually, in a community sample being treated for PTSD. Compared to waitlist controls, the CBT-I group had a superior response on all sleep diary measures, on sleep quality assessed with the Pittsburgh Sleep Quality Index (PSQI), and on polysomnographically derived total sleep time; these effects remained significant at 6-month follow-up. Insomnia assessed with the ISI remitted in 41 % of the CBT-I group. However, both the CBT-I group and waitlist controls reported reductions in PTSD symptom severity and post-traumatic nightmares. Trials with an active treatment control group are required to establish the relation of these responses to the therapeutic elements of CBT-I specifically.

Psychotherapeutic Treatments for Nightmares in PTSD

Imagery rehearsal (IR; [60, 73, 74]) is the best studied psychotherapeutic intervention for recurrent nightmares. There is evidence that it leads to increased mastery of nightmare content and experience [75]. A variety of treatment protocols that share the following basic steps of IR have been studied: choosing a repetitive nightmare, rescripting it during waking, and imaginally rehearsing the new dream script at bedtime. IR treatment protocols differ widely in the type of nightmare to target for treatment, the extent of exposure to nightmare content, the individual guidance given by therapists to aid in rescripting, and the delivery format (individual or group) [76–78]. In addition, most forms of IR include additional potentially active treatment elements, such as CBT-I techniques.

Two recent meta-analyses statistically summarized the results of IR treatments for post-traumatic nightmares [74, 79], combining data from predominantly uncontrolled trials. They reported large effect sizes for nightmare frequency, sleep quality, and overall PTSD symptomatology. Casement and Swanson [79] also found that the effects were maintained at six and 12 months post-treatment. It is important to note that these meta-analyses combined results from a variety of treatment protocols and diverse post-traumatic populations (not necessarily diagnosed with PTSD), two important factors in treatment outcome [78].

Only two RCTs of IR for post-traumatic nightmares included potentially active control groups [80, 81]. In one study of Vietnam War Veterans with chronic, severe PTSD and recurrent nightmares [80], there was no significant difference in reducing nightmare frequency and PTSD severity and improving sleep quality between IR and a comparison treatment that incorporated elements of CBT-I. In the other RCT [81], both treatment groups (i.e., prazosin vs. behavioral sleep intervention), compared to a placebo control group, showed greater improvement in insomnia and PTSD severity. Harb and colleagues [78] have emphasized the limitations of the extant IR literature and identified strategies for advancing the field. In particular, Consolidated Standards of Reporting Trials (CONSORT) guidelines for conducting and reporting on trials should be followed in all clinical trials, and differences among treatment protocols and study populations be considered. Although not different from rates for other CBTs for PTSD [82], dropout rates for IR therapy range from 25 to 40 % [61]. It will be important to delineate the factors contributing to dropout as well as treatment success, as they may hold clues to optimizing the utilization of IR.

Exposure, relaxation, and rescripting therapy (ERRT) is a variant of IR that has shown promise for reducing nightmares and insomnia in predominantly civilian samples with post-traumatic symptoms [77, 83–85]. In an uncontrolled study in Veterans (N=37) that used imagery rescripting and exposure therapy (IRET), a variant of ERRT, Long and colleagues [86] showed reductions in nightmare frequency and PTSD severity and increased sleep time . Of interest for understanding the biological substrates of ERRT, Rhudy and colleagues [85] showed significant reductions with treatment in subjective and physiological (skin conductance, heart rate, facial electromyogram) reactions to nightmare-related content; these changes were maintained at 6-month follow-up.

Combined Psychotherapeutic Interventions for Insomnia and Nightmares in PTSD

Combining CBT-I and IR is intuitively appealing due to the prevalence of both insomnia and recurrent nightmares in PTSD. Accordingly, several integrated therapies have been developed. Krakow and colleagues [87] examined the efficacy of a combination treatment ("sleep dynamic therapy") in an uncontrolled study of 62 crime victims with PTSD. There were significant reductions in nightmares and PTSD severity and an improvement in sleep quality, but all outcome measures remained in the clinically significant range post-treatment. Crime victims treated with components of CBT-I and IR in a small uncontrolled trial showed a moderate improvement in sleep quality and a decrease in nightmare frequency, as well as a reduction in overall PTSD severity [88]. Veterans with PTSD, treated with components of CBT-I and IR in an uncontrolled investigation, had a reduction in insomnia, nightmare frequency, and nightmare distress [89]. In a recent meta-analysis of studies of CBT-I combined with IR, a large gain in sleep quality was reported; however, combined treatment did not significantly improve outcomes for PTSD severity and nightmares [79]. In summary, in the service of improving both the insomnia and nightmare problems related to PTSD, a combination of IR and CBT-I appears to be a promising treatment approach for many individuals.

Pharmacological Treatments for PTSD

The selective serotonin reuptake inhibitors (SSRIs) have the strongest evidence base among pharmacotherapies for PTSD [58, 90]. Two SSRIs, paroxetine and sertraline, are FDA-approved for this indication, although there is little evidence that they are superior to other medications of their class. The use of selective norepinephrine-serotonin reuptake inhibitors (SNRIs), in particular venlafaxine, is also supported by clinical guidelines [90]. However, there is remarkably little evidence that insomnia and recurrent nightmares in PTSD respond to the SSRIs and SNRIs.

In a controlled trial of the SSRI sertraline for PTSD [91], the drug produced a 60 % response compared to 38 % with placebo; however, the change in the PSQI score was not greater with drug compared to placebo. In another trial [92], individuals receiving sertraline had a 53 % response rate compared to a 32 % placebo response; however, insomnia was the only adverse effect that occurred at a greater than placebo incidence. The SSRI paroxetine was reported to be effective for the acute treatment (12 weeks) of chronic PTSD, with a 62 % response rate compared to a 37 % placebo response; there was an improvement in all three PTSD symptom clusters; sleep quality was not assessed [93]. In a small open-label trial in Vietnam War combat Veterans, the SSRI fluvoxamine led to an improvement in "PTSD symptoms and all domains of subjective sleep quality" [94]. Of particular interest, dreams related to a combat trauma, which have been viewed as specific to PTSD [28], were reduced more than "generic unpleasant dreams" [94].

Although there is support from randomized controlled trials for the efficacy of the SNRI venlafaxine in treating PTSD, Davidson and colleagues [95] found no significant improvement in the hyperarousal symptom cluster, which includes insomnia. Stein and colleagues [96] did a pooled analysis of two randomized, double-blind, placebo-controlled trials and found no advantage of venlafaxine ER in reducing distressing dreams as assessed with the CAPS-SX17. Accordingly, the *Best Practice Guide for the Treatment of Nightmare Disorder in Adults* does not recommend venlafaxine for treating PTSD-associated nightmares [73].

The tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) have not been the subject of large randomized clinical trials for the treatment of PTSD [97]. There is only a low-level evidence for the usefulness of the TCAs in controlling recurrent nightmares [73]. Similarly, there is only a weak support for the usefulness of a MAOI, phenelzine, in ameliorating the nightmare disturbance in PTSD; this despite the prominent REM (rapid eye movement) sleep suppressant effect of the MAOIs and the evidence that most nightmares emerge from REM sleep [73].

The atypical antipsychotic drugs have been investigated as a treatment for PTSD. In a randomized placebo-controlled trial, individuals with non-combat-related PTSD treated with olanzapine monotherapy showed an overall greater reduction in the CAPS score, but only improvement in the Criterion C symptom cluster (avoidance and numbing) reached statistical significance [98]. Therefore, larger studies will be required to determine whether olanzapine alone can ameliorate the reexperiencing symptoms (including recurrent nightmares) and the hyperarousal symptoms (including insomnia) of PTSD. A small placebo-controlled trial of adjunctive olanzapine for combat-related PTSD non-responsive to SSRI

treatment found a greater improvement in sleep, as measured by the PSQI, in the olanzapine group [99].

Among the atypical antipsychotic drugs, the greatest number of randomized placebo-controlled trials for PTSD has been carried out with adjunctive risperidone [100]. Although the largest study, in Veterans, showed no significant effect [101], an advantage for risperidone in reducing the total CAPS score and the Criterion D scale score was found in another investigation of combat-related PTSD [102] and in a study of women with PTSD related to childhood abuse [103]. There have been no completed RCTs of quetiapine, ziprasidone, and aripiprazole in PTSD populations.

Pharmacological Treatments for Insomnia in Post-Traumatic Stress Disorder

Few studies have examined the benefits of pharmacotherapy for insomnia in individuals with PTSD [104]. Cates and colleagues [105] reported no significant advantage of the benzodiazepine clonazepam in a small, single-blind, placebo-controlled trial, which the investigators recognized as under powered. Clonazepam, the mainstay of pharmacological treatment for RBD [73], may have a place in the treatment of excessive movement during sleep in PTSD, a topic for future research.

In a series of case reports, the novel non-benzodiazepine benzodiazepine receptor agonist (NBRA) zolpidem was noted to be beneficial for insomnia related to PTSD [106]. In some cases, improvements in insomnia and nightmares were sustained for more than a year. In a randomized, double-blind, placebo-controlled trial, Pollack and colleagues [107•] found that a 3-week treatment with the NBRA eszopiclone led to greater improvements in PTSD symptoms including sleep disturbance.

The 5-HT_2 antagonist/SSRI trazodone, an antidepressant drug with prominent sedative properties, is often used in low doses for treating insomnia [108]. Combining trazodone with an SSRI is a common strategy for treating insomnia comorbid with depression [109]. Of a group of inpatients with PTSD, 80 % had been treated with trazodone, and of these, 72 % had found the drug helpful in decreasing nightmares and reducing the latency to sleep onset [110]. In a study of Vietnam War Veterans with PTSD, trazodone improved sleep, among a range of symptoms, after 2 to 3 months [111]. In a small group of individuals with war trauma-associated PTSD, nefazodone, another antidepressant that is a potent 5-HT_2 antagonist, led to a change in dream content from trauma- to non-trauma-related [112]. Although nefazodone is no longer widely used because of a concern about hepatotoxicity, this finding suggests that 5-HT_2 antagonism may be important in nightmare suppression.

Pharmacological Treatments for Nightmares in Post-Traumatic Stress Disorder

1As noted above, fluvoxamine, trazodone, and nefazodone may have some utility in treating the nightmare disturbance in PTSD. However, none of these drugs has been tested in a randomized controlled trial. Other drugs for which there is low level evidence of usefulness for recurrent nightmares are topiramate, low-dose cortisol, and gabapentin [73]. Several case series provide conflicting data on the benefit of cyproheptadine [73]. Arguably, the most important advance in the pharmacotherapy of the nightmare disturbance in PTSD has been the introduction of prazosin, an alpha-1 adrenoceptor antagonist that is FDA-approved for the treatment of hypertension in the U.S. Raskind [113] reported the first positive open-label trial of this drug in 2000. The first placebo-controlled trial of prazosin, carried out with a crossover design in U.S. military Veterans, reported a decrease in nightmares and an improvement in sleep quality [114]. A larger, placebo-controlled, parallel group study in Veterans with chronic PTSD confirmed the beneficial effect of prazosin in reducing nightmares and sleep disturbance [115]. A smaller placebo-controlled trial in civilians with PTSD also demonstrated an advantage of prazosin in reducing trauma nightmares [116]. Raskind and colleagues [117•] reported a decrease in combat-related nightmares in active-duty U.S. service members treated with prazosin compared to placebo; sleep quality and overall PTSD symptoms were improved as well. In a retrospective chart review study in Veterans with PTSD, prazosin led to a decrease in the number of non-nightmare-distressed awakenings, i.e., awakenings accompanied by extreme psychological distress without any recall of dream mentation [118].

1Prazosin is generally well tolerated. An alpha-1 adrenoceptor antagonist, it can be associated with lightheadedness, orthostatic hypotension in particular. To minimize the latter problem, treatment is initiated at a dose of 1 mg hs, titrated upward every few days consistent with any reported side effects. The mean final dose in extant randomized clinical trials was in the range of 3 to 13 mg hs [114–116, 117•]. Individuals using a phosphodiesterase inhibitor for erectile dysfunction should be cautioned to separate the administration of the two medications by approximately 5 h in order to avoid additive hypotensive effects. Prazosin must be administered continuously to avoid the recurrence of nightmares; it is not known whether there could be a lasting beneficial effect after drug discontinuation.

It has been suggested that other drugs that reduce central noradrenergic activity might also ameliorate the nightmare disturbance in PTSD. There are positive case reports for clonidine, an alpha-2 adrenoceptor agonist that inhibits the firing

of noradrenergic locus coeruleus neurons. Clonidine was reported to be useful in treating post-traumatic nightmares in two Veterans with combat-related trauma [119], but no clinical trial of this drug has been conducted.

Conclusions

Chronic insomnia and recurrent nightmares are among the most distressing symptoms of PTSD, and evidence suggests that they are a core feature of the disorder [1, 61]. Other sleep disorders, including OSA, PLMD, and RBD, and other mental disorders may be comorbid with PTSD and have implications for successful treatment. Relatively few studies have directly investigated the effects of specific interventions on sleep disturbances in PTSD.

Psychotherapeutic interventions designed specifically to treat chronic insomnia and recurrent nightmares, CBT-I and IR, respectively, have shown promise and are considered first-line treatments. However, the majority of psychotherapy studies used some combination of CBT-I and IR, complicating efforts to identify the process by which each treatment achieves its effects. Better controlled studies that use a specific intervention and include an active treatment control group are needed to determine more definitively the efficacy of CBT-I and IR for the sleep disturbances in PTSD.

Pharmacological interventions for the overall PTSD symptom complex rarely have examined the efficacy of treatment for chronic insomnia and recurrent nightmares. Two SSRIs, paroxetine and sertraline, are FDA-approved for the treatment of PTSD; however, there is limited evidence that chronic insomnia and post-traumatic nightmares respond to these drugs. Although benzodiazepines are commonly prescribed for insomnia, they are not recommended due to the potential for dependence [120]. The alpha-1 adrenoceptor antagonist prazosin is the only pharmacological intervention for post-traumatic nightmares that received a grade of "recommended" by the AASM's best practice guidelines [73].

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Compliance with Ethics Guidelines

Conflict of Interest Janeese A. Brownlow, Gerlinde C. Harb, and Richard J. Ross declare that they have no conflict of interest.

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